D E C L A R A T I O N

I, Kumi HIRANO, declare and say:

that I am thoroughly conversant with both the Japanese and English languages;

that I am presently engaged as a translator in these languages; and,

that the attached document represents a true English translation of the complete specification and claim(s) originally filed as Japanese Patent Application No. 1999-26691 filed on February 3, 1999.

I further declare that all statements made herein of my own knowledge are true; and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: November 11, 2002

Kumi HIRANO

1999-26691

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(Translation)

SPECIFICATION 11-26691

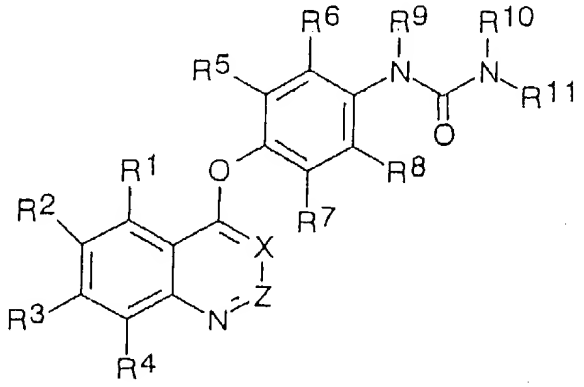
1. TITLE OF THE INVENTION

QUINOLINE DERIVATIVES AND QUINAZOLINE DERIVATIVES

2. CLAIMS:

1. Compounds represented by formula (1) or a pharmaceutically acceptable salt or solvate thereof:

[Chemical Formula 1]



(I)

wherein

X and Z each represent CH or N;

R^1, R^2, and R^3, which may be the same or different, represent a hydrogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkenyl, C_{1-6} alkynyl, nitro, or amino, which C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkenyl, and C_{1-6} alkynyl are optionally substituted by a halogen atom; C_{1-4} alkoxy; amino (which amino is optionally substituted by C_{1-4} alkyl optionally substituted by C_{1-4} alkoxy), or is optionally substituted by three- to seven-membered carbocyclic or heterocyclic group;

R^4 represents a hydrogen atom;

R^5, R^6, R^7, and R^8, which may be the same or different, represent a hydrogen atom, a halogen atom, C_{1-4} alkyl, C_{1-3} alkoxy, C_{1-3} alkylthio, nitro, or amino, provided that R^5, R^6, R^7, and R^8 do not simultaneously represent a hydrogen atom;

R^9 and R^{10}, which may be the same or different, represent a hydrogen atom or C_{1-4} alkyl, C_{1-4} alkyl is optionally substituted by a halogen atom; C_{1-4} alkoxy; amino (which amino is optionally substituted by C_{1-4} alkyl optionally substituted by C_{1-4} alkoxy); or a saturated or unsaturated three- to seven-membered cabocyclic or heterocyclic group; and

R^{11} represents C_{1-6} alkyl, C_{1-6} alkenyl, or C_{1-6} alkynyl (which C_{1-6} alkyl, C_{1-6} alkenyl, and C_{1-6} alkynyl each are optionally substituted by a halogen atom or C_{1-6} alkoxy), or

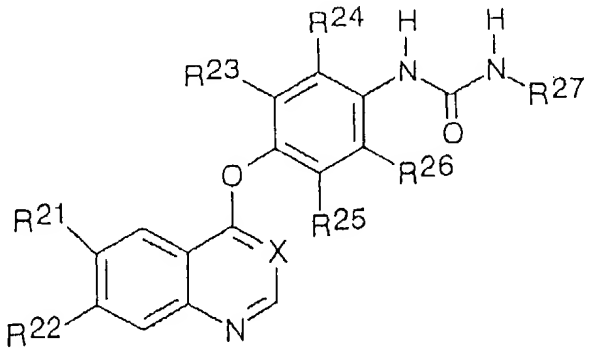
$-(CH_2)m-R^{12}$ wherein m is an integer of 0 to 4 and R^{12} represents a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group which is optionally substituted by a halogen atom, C_{1-6} alkyl or C_{1-6} alkoxy and is optionally condensed with other saturated or unsaturated three- to seven-membered carbocyclic ring or heterocyclic ring to form a bicyclic ring.

2. The compound according to claim 1, wherein R^1, R^9, and R^{10} represent a hydrogen atom.

3. The compound according to claim 1, wherein X represents N or CH and Z represents CH.

4. Compounds represented by formula (Ia) or a pharmaceutically acceptable salt or solvate thereof:

[Chemical Formula 2]



(Ia)

wherein:

X represents CH or N;

R^{21} and R^{22}, which may be the same or different, represent a hydrogen atom or C_{1-4} alkoxy, which C_{1-4} alkoxy is optionally substituted by C_{1-4} alkoxy or saturated or unsaturated five- or six-membered carbocyclic ring or heterocyclic ring;

R^{23}, R^{24}, R^{25}, and R^{26}, which may be the same or different, represent a hydrogen atom, a halogen atom, C_{1-4} alkyl, C_{1-3} alkoxy, C_{1-3} alkylthio, nitro, or amino, provided that R^{23}, R^{24}, R^{25}, and R^{26} do not simultaneously represent a hydrogen atom;

R^{27} represents C_{1-6} alkyl, or C_{1-6} alkenyl, C_{1-6} alkynyl, which C_{1-6} alkyl, C_{1-6} alkenyl, or C_{1-6} alkynyl is optionally substituted by a halogen atom or C_{1-4} alkoxy, or $-(CH_2)n-R^{28}$ wherein n is an integer of 0 to 4 and R^{28} represents a saturated or unsaturated six-membered carbocyclic or heterocyclic group which is optionally substituted by a halogen atom, C_{1-4} alkyl or C_{1-4} alkoxy and is optionally condensed with other saturated or unsaturated five- or six-membered carbocyclic ring or heterocyclic ring to form a bicyclic ring.

5. The compound according to claim 4 wherein:

C_{1-4} alkoxy optionally represented by R^{21} and R^{22} is optionally substituted by C_{1-4} alkoxy or saturated or unsaturated six-membered carbocyclic ring or heterocyclic ring;

The saturated or unsaturated six-membered carbocyclic group or heterocyclic group ring represented by R^{28} is optionally condensed with other saturated or unsaturated six-membered carbocyclic or heterocyclic ring to form a bicyclic ring.

6. The compound according to claim 4 wherein any one of R^{23}, R^{24}, R^{25} and R^{26} represents a halogen atom.

7. The compound according to claim 4, wherein any one of R^{23}, R^{24}, R^{25}, and R^{26} represents a chlorine atom.

8. The compound according to claim 4, wherein any one of R^{23}, R^{24}, R^{25}, and R^{26} represents C_{1-4} alkyl.

9. The compound according to claim 4, wherein two of R^{23}, R^{24}, R^{25}, and R^{26} represent methyl and the other two represent a hydrogen atom.

10. The compound according to claim 4, wherein any one of R^{23}, R^{24}, R^{25}, and R^{26} represents nitro, amino, C_{1-3} alkoxy, or C_{1-3} alkylthio.

11. The compound according to claim 4, wherein:

X represents N;

R^{21} and R^{22} represent C_{1-4} alkoxy which is optionally substituted by C_{1-4} alkoxy or saturated or unsaturated five- or six-membered carbocyclic or heterocyclic ring;

R^{23}, R^{24}, and R^{25} represent a hydrogen atom;

R^{26} represents a halogen atom, C_{1-4} alkyl, or nitro; and

R^{27} represents C_{1-6} alkyl, C_{1-6} alkenyl, or C_{1-6} alkynyl which C_{1-6} alkyl, C_{1-6} alkenyl, or C_{1-6} alkynyl is optionally substituted by a halogen atom or C_{1-4} alkoxy or $-(CH_2)n-R^{28}$ wherein n represents integer 0 or 1 and R^{28} represents phenyl, pyridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substitued by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy.

12. The compound selected from the group consisting of the following compounds, or a pharmaceutically acceptable salt or solvate thereof:

1. N-(2, 4-difluorobenzil)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}urea;
2. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(2-fluoroethyl)urea;
3. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(2-pyridyl)urea;
4. N-aryl-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}urea;
5. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-propylurea;
6. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(4-fluorobutyl)urea;
7. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(2-propynyl)urea;

8. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-ethylurea;

9. N-butyl-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}urea;

10. N-(sec-butyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}urea;

11. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-isobutylurea;

12. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(1, 2-dimethylpropyl) urea;

13. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)-oxy]phenyl}-N'-propylurea;

14. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(4-fluoro-2-methylphenyl)urea;

15. N-(5-bromo-6-methyl-2-pyridyl))-N'-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)-oxy]phenyl}urea;

16. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-chloro-2-pyridyl) urea;

17. N-(5-bromo-2-pyridyl)-N'-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl} urea;

18. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2-methoxyphenyl)urea;

19. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2-methylphenyl)urea;

20. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-2- pyridyl) urea;

21. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(6-methyl-2-pyridyl) urea;

22. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(4-methxyphenyl)urea;

23. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(1-naphthyl)urea;

24. N-(2, 4-difluorophenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}urea;

25. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(4-fluoro-2-methylphenyl)urea;

26. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(3-fluoro-2-methylphenyl)urea;

27. N-(6-bromo-6-methyl-2-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinoryl)oxy]-2,

3-dimethylphenyl}urea;

28. N-(5-chloro-2-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinoryl)oxy]-2, 3-dimethylphenyl} urea;

29. N-(5-bromo-2-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinoryl)oxy]-2, 3-dimethylphenyl} urea;

30. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(2-methoxyphenyl)urea;

31. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(2-methylphenyl)urea;

32. N-(4-chloro-2-methylphenyl)-N'-{4-[(6, 7-dimethoxy-4-quinoryl)oxy]-2, 3-dimethylphenyl}urea;

33. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(2-pyridyl)urea;

34. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'- (5-methyl-2-pyridyl)urea;

35. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(6-methyl-2-pyridyl)urea;

36. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'- (4-methxyphenyl) urea;

37. N-(2, 4-difluorophenyl)-N'-{4-[(6, 7-dimethoxy-4-quinoryl)oxy]-2, 5-dimethylphenyl}urea;

38. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-propylurea;

39. N-(4-chloro-2-methylphenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}urea;

40. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(4-fluoro-2-methylphenyl)urea;

41. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(3-fluoro-2-methoxylphenyl)urea;

42. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(2-methylphenyl)urea;

43. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(2-

methoxylphenyl)urea;

44. N-(5-bromo-6-methyl-2-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}urea;

45. N-(2, 6-dimethoxy-3-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}urea;

46. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(4-methoxyphenyl)urea;

47. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-nitrophenyl}-N'-propylurea;

48. N-(2, 4-difluorophenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-nitrophenyl}urea;

49. N-{3. 5-dichloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2, 4-difluorophenyl)urea;

50. N-(2, 4-difluorophenyl)-N'-(2-fluoro-4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}phenyl)urea;

51. N-(2-chloro-4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}phenyl)-N'-(2, 4-difluorophenyl)urea;

52. N-(2, 4-difluorophenyl)-N'-(4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}-2, 5-dimethylphenyl)urea;

53. N-(4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}-2, 5-dimethylphenyl)-N'- (2-methoxyphenyl)urea;

54. N-(2-chloro-4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}phenyl)-N'-(2, 4-difluorophenyl)urea;

55. N-(2-chloro-4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}phenyl)-N'-(2-methoxyphenyl)urea;

56. N-(2,4-difluorophenyl)-N'-(4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]-oxy}-2, 3- dimethylphenyl)urea;

57. N-(4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}-2, 3-dimethylphenyl)-N' -(2-methoxyphenyl)urea;

58. N-(2, 4-difluorophenyl)-N'-(4-{[6-methoxy-7-(2-methoxyethoxy) -4-quinolyl]-oxy}-2, 5-dimethylphenyl)urea;

59. N-(4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}-2, 5-dimethylphenyl)-N'- (2-methoxyphenyl)urea;

60. N-(4-{[7-(benzyloxy)-6-methoxy-4-quinolyl]oxy}-2, 3-dimethylphenyl)-N'-(2-methoxyphenyl)urea;

61. N-{2-chloro-4-[(6, 7-dimethosy-4-quinazolinyl)oxy]phenyl}-N'-(2, 4-diflurophenyl) urea;

62. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea;

63. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-ethylurea;

64. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-isobutylurea;

65. N-butyl-N'-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}urea;

66. N-aryl-N'-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}urea;

67. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-pentylurea; and

68. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-(2-propylny)urea.

13. A pharmaceutical composition comprising the compound according to any one of claims 1 to 12 or pharmaceutically acceptable salt or solvate thereof.

14. A pharmaceutical composition according to claim 12 used in the treatment of a disease selected from a group comprising tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma.

[Detailed Description of the Invention]

[0001]

[Background of the Invention]

Field of the Invention

[0001]

The present invention relates to quinoline derivatives and quinazoline derivatives having antitumor activity. More particularly, the present invention relates to quinoline derivatives and quinazoline derivatives that are useful for the treatment of diseases such as tumor, diabetic retinopaphy, chronic rheumatism, psoriasis,

atherosclerosis, and Kaposi's sarcoma.

[0002]

Background Art

WO 97/17329 describes quinoline derivatives and quinazoline derivatives having antitumor activity. WO 97/17329 however, describes neither the effects of these quinline derivatives and quinazoline derivatives on cyromorphsis nor the compounds according to the present invention.

[0003]

[Summary of the Invention]

The present inventors have found that a group of quinoline derivatives and quinazoline derivatives has antitumor activity and, at the same time, has no significant effect on cytomorphsis.

[0004]

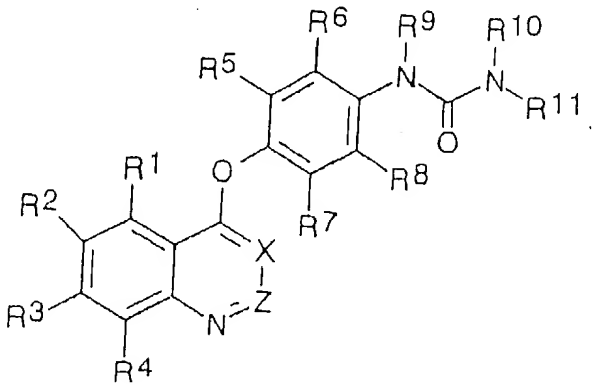
The object of the present invention is to provide compounds which have antitumor activity and, at the same time, have no significant effect on cytomorphosis. The activity of increasing the cell size may be regarded as activity of including tissue disorders.

[0005]

According to the present invention, there is provided a compound represented by formula (I) or a pharmaceutically acceptable salt or solvate thereof:

[0006]

[Chemical Formula 3]



(I)

wherein

X and Z each represent CH or N;

R^1, R^2, and R^3, which may be the same or different, represent a hydrogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkenyl, C_{1-6} alkynyl, nitro, or amino, which C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkenyl, and C_{1-6} alkynyl are optionally substituted by a halogen atom; C_{1-4} alkoxy; amino which is optionally substituted by C_{1-4} alkyl optionally substituted by C_{1-4} alkoxy; or saturated or unsaturated three- to seven-carbocyclic or heterocyclic group;

R^4 represents a hydrogen atom;

R^5, R^6, R^7, and R^8, which may be the same or different, represent a hydrogen atom, a halogen atom, C_{1-4} alkyl, C_{1-3} alkoxy, C_{1-3} alkylthio, nitro, or amono, provided that R^5, R^6, R^7, and R^8 do not simultaneously represent a hydrogen atom;

R^9 and R^{10}, which may be the same or different, represent a hydrogen atom, C_{1-4} alkyl, C_{1-4} alkyl is optionally substituted by a halogen atom; C_{1-4} alkoxy; amino which is optionally substituted by C_{1-4} alkyl optionally substituted by C_{1-4} alkoxy; or a suturated or unsaturated three- to seven-membered carbocyclic or hererocyclic group; and

R^{11} represents C_{1-6} alkyl, C_{1-6} alkenyl, or C_{1-6} alkynyl (which C_{1-6} alkyl, C_{1-6} alkenyl, and C_{1-6} alkynyl each are optionally substituted by a halogen atom or C_{1-6} alkoxy), or $-(CH_2)m-R^{12}$ wherein m is an integer of 0 to 4 and R^{12} represents a saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic group which is optionally substituted by a halogen atom, C_{1-6} alkyl, or C_{1-6} alkoxy and is optionally condensed with other saturated or unsaturated three- to seven-membered carbocyclic ring or heterocyclic ring to form a bicyclic ring.

The compounds according to the present invention is useful, for example, for the treatment of tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, Kaposi's sarcoma, and solid tumor.

[0007]

[Detailed Description of the Invention]

Compound

As used herein, the term "C_{1-6} alkyl", "C_{1-6} alkoxy", "C_{1-6} alkenyl" and "C_{1-6} alkynyl" as a group or a part of a group respectively mean straight chain or branched chain alkyl, alkoxy, alkenyl and alkynyl having 1 to 6, preferably 1 to 4 carbon atom.

[0008]

Examples of C_{1-6} alkyl include methyl, ethyl, n-propyl, isopropyl, n-bubyl, i-butyl, s-butyl, t-butyl, n-pentyl, n-hexyl.

[0009]

Examples of C_{1-6} alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, and t-butoxy.

[0010]

Examples of C_{1-6} alkenyl include allyl, butenyl, pentenyl and hexenyl.

[0011]

Examples of C_{1-6} alkynyl include 2-propynyl, butynyl, pentynyl and hexynyl.

[0012]

The term "halogen atom" means a fluorine, chlorine, bromine, or iodine atom.

[0013]

The saturated or unsaturated three- to seven-membered carbocyclic or heterocyclic ring is preferably five- to seven-membered, more preferebly five- or six-membered, saturated or unsaturated carbocyclic or heterocyclic ring.

[0014]

Examples of saturated or unsaturated three- to seven-membered carbocyclic group include phenyl, cycloheptyl, cyclohexyl, and cyclopentyl.

[0015]

The saturated or unsaturated three- to seven-membered heterocyclic ring contains at least one hetero-atom selected from oxygen, nitrogen, and sulfur atoms. The term "hetero-atom" used herein means an oxygen, nitrogen, or sulfur atom. Examples of saturated or unsaturated three- to seven-membered heterocyclic groups

include pyridyl, piperidino, morphlino, piperidinyl, morphorinyl, imidazolyl, oxaxolyl, thiazolyl, pyrrolidinyl, piperadinyl, and pyrazolyl.

[0016]

The saturated or unsaturated heterocyclic group, which may be represented by R^{12} and R^{28}, may be condensed with other saturated or unsaturated heterocyclic ring to form a bicyclic ring. Such condensed cyclic groups include naphthyl, indanyl, quinolyl, and quinazolinyl.

[0017]

R^1, R^2, and R^3 preferably represents a hydrogen atom or optionally substituted C_{1-4} alkoxy. C_{1-4} alkoxy may be preferably substituted by methoxy, a saturated or unsaturated six-membered carbocyclic group (specially, phenyl) or a five- or six-membered heterocyclic ring (specially, morphlino) containing a saturated or unsaturated nitrogen atom and/or oxygen atom.

[0018]

Examples of preferable combination of R^1, R^2, and R^3 include:

R^1 preferably represents a hydrogen atom, and R^2 and R^3 preferably represent C_{1-4} alkoxy; or

R^1 preferably represents a hydrogen atom, R^2 represents C_{1-4} alkoxy, and R^3 preferably represents C_{1-4} alkoxy (more preferably, methoxy), saturated or unsaturated five- or six-membered carbocyclic group (more preferably, phenyl), or

C_{1-4} alkoxy substituted by saturated or unsaturated nitrogen atom and/or five- or six-membered heterocyclic group containing a oxygen atom (more preferebly, morpholino).

[0019]

Examples of preferable combination of R^5, R^6, R^7, and R^8 include:

R^5, R^6, and R^7 represent a hydrogen atom and R^8 represents a halogen atom (more preferably, a chlorine atom);

R^5 and R^6 represent a hydrogen atom and R^7 and R^8 represent C_{1-4} alkyl (more preferably, methyl);

R^5 and R^8 represent a hydrogen atom and R^6 and R^7 represent C_{1-4} alkyl (more

preferably, methyl); and

R^5, R^7, and R^8 represent a hydrogen atom and R^6 represents nitro or amino.

[0020]

R^9 and R^{10} preferably represent a hydrogen atom, methyl, ethyl, or benzyl, more preferably R^9 and R^{10} together represent a hydrogen atom.

[0021]

$-(CH_2)m-R^{12}$ which may be represented by R^{11} wherein m preferably represents an integer of 0 to 2, more preferably 0 or 1. Preferable examples of R^{12} include:

saturated or unsaturated six-membered carbocyclic group (more preferably, phenyl) which may be substituted; and six-membered heterocyclic group (more preferably, pyridyl) containing saturated or unsaturated nitrogen atom and/or an oxygen atom which may be substituted.

A group of preferred compounds represented by formula (I) includes compounds wherein R^1, R^9, and R^{10} represent a hydrogen atom.

[0022]

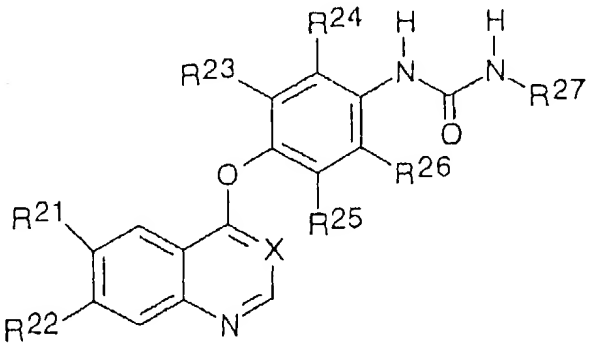
A group of preferred compounds represented by formula (I) includes compounds wherein X represents N or CH and Z represents CH.

[0023]

Another group of preferred compound represented by formula (I) includes compounds represented by formula (Ia).

[0024]

[Chemical Formula 4]



(Ia)

wherein

X represents CH or N;

R^{21} and R^{22}, which may be the same or different, represent a hydrogen atom or C_{1-4} alkoxy and C_{1-4} alkoxy may be substituted by saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group;

R^{23}, R^{24}, R^{25}, and R^{26}, which may be the same or different, represent a hydrogen atom, a halogen atom, C_{1-4} alkyl, C_{1-3} alkoxy, C_{1-3} alkylthio, nitro, or amino, provided that R^{23}, R^{24}, R^{25}, and R^{26} do not simultaneously represent a hydrogen atom; and

R^{27} represents C_{1-6} alkyl, C_{1-6} alkenyl, or $C1_{-6}$ alkynyl (which C_{1-6} alkyl, C_{1-6} alkenyl, and C_{1-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or -(CH_2)-n-R^{28} wherein n is an integer of 0 to 4 and R^{28} represents a saturated or unsaturated six-membered carbcyclic or heterocyclic group which is optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy and is optionally condensed with other saturated or unsaturated five- or six-membered carbocyclic or heterocyclic ring to form a bicyclic ring.

R^{21} and R^{22} preferably represent a hydrogen atom or C_{1-4} alkoxy which may be substituted. C_{1-4} alkoxy is preferably substituted by C_{1-4} alkoxy or saturated or unsaturated six-membered carbocyclic or heterocyclic group, more preferably methoxy, saturated or unsaturated six-membered carbocyclic group (specially, phenyl) or six-membered heterocyclic group (specially, morphlino) containing a saturated or unsaturated nitrogen atom and/or oxygen atom.

[0025]

More preferable combinations of R^{21} and R^{22} include:

R^{21} and R^{22} represent C_{1-4} alkoxy; and

R^{21} represent C_{1-4} alkoxy and R^{22} represents C_{1-4} alkoxy substituted by methoxy, phenyl, or morpholyl.

[0026]

More preferable combinations of R^{23}, R^{24}, R^{25} and R^{26} include:

R^{23}, R^{24}, and R^{25} represent a hydrogen atom and R^{26} represents a halogen atom (more preferably, chlorine atom);

R^{23} and R^{24} represent a hydrogen atom and R^{25} and R^{26} represent C_{1-4} alkyl (more preferably, methyl);

R^{23} and R^{26} represent a hydrogen atom and R^{24} and R^{26} represent C_{1-4} alkyl (more preferably, methyl);

R^{23}, R^{25}, and R^{26} represent a hydrogen atom and R^{24} represents nitro, amino, C_{1-3} alkoxy, or C_{1-3} alkylthio.

[0027]

$-(CH_2)n-R^{28}$ which may be represented by R^{27} wherein n preferably represent an integer of 0 to 2, more preferably an integer of 0 or 1. Preferable examples of R^{28} include phenyl which may be substituted and six-membered heterocyclic group (more preferably, pyridyl) containing a saturated or unsaturated nitrogen atom and/or oxygen atom which may be substituted. Saturated or unsaturated six-membered carbocyclic group or heterocyclic group may preferably be condensed with other saturated or unsaturated six-membered carbocyclic ring or heterocyclic ring to form a bicyclic ring.

[0028]

Examples of preferred compounds represented by formula (Ia) include:

compounds wherein

X represents N;

R^{21} and R^{22} represent C_{1-4} alkoxy optionally substituted by C_{1-4} alkoxy or a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group;

R^{23}, R^{24}, and R^{25} represent a hydrogen atom;

R^{26} represents a halogen atom, C_{1-4} alkyl or nitro, more preferably, chlorine atom;

R^{27} represents C_{1-6} alkyl, C_{1-6} alkenyl, or C_{1-6} alkynyl (which C_{1-6} alkyl, C_{1-6} alkenyl, and C_{1-6} alkynyl each are optionally substituted by a halogen atom or C_{1-4} alkoxy), or $-(CH_2)n-R^{28}$ wherein n is an integer of 0 or 1 and R^{28} represents phenyl, piridyl, or naphthyl which phenyl, pyridyl, and naphthyl are optionally substituted by a halogen atom, C_{1-4} alkyl, or C_{1-4} alkoxy, more preferably C_{3-4} alkyl, C_{3-4} alkenyl, and or C_{3-4} alkynyl optionally substituted.

[0029]

Preferred examples of compounds according to the present invention include the following compounds.

1. N-(2, 4-difluorobenzil)-N'-{4-[(6, 7-dimethoxy-4-quinoryl)oxy]-2-fluorophenyl} urea;
2. N-{4-[(6, 7-dimethoxy-4-quinoryl)oxy]-2-fluorophenyl}-N'-(2-fluoroethyl)urea;
3. N-{4-[(6, 7-dimethoxy-4-quinoryl)oxy]-2-fluorophenyl}-N'-(2-pyridylmethyl)urea;
4. N-allyl-N'-{4[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}urea;
5. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-propylurea;
6. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(4-fluorobutyl)urea;
7. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(2-propynyl)urea;
8. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-ethylurea;
9. N-butyl-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}urea;
10. N-(sec-butyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}urea;
11. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-isobutylurea;
12. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(1, 2-diomethylpropyl)urea;
13. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-propylurea;
14. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(4-fluoro-2-methylphenyl)urea;
15. N-(5-bromo-6-methyl-2-pyridyl)-N'-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)-oxy]phenyl}urea;
16. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-chloro-2-pyridyl) urea;
17. N-(5-bromo-2-pyridyl)-N'-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}urea;
18. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2-methoxyphenyl) urea;
19. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2-methylphenyl) urea;

20. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-methyl-2-pyridyl) urea;

21. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(6-methyl-2-pyridyl) urea;

22. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(4-methoxyphenyl) urea;

23. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(1-naphthyl)urea;

24. N-(2, 4-diofluorophenyl)-N'-{4[(6, 7-dimethoxy-4-quinolyl)oxy]-2,3-dimethylphenyl}urea;

25. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(4-fluoro-2-methylphenyl)urea;

26. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(3-fluoro-2-methoxyphenyl)urea;

27. N-(5-bromo-6-methyl-2-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}urea;

28. N-(5-chloro-2-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl} urea;

29. N-(5-bromo-2-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl} urea;

30. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(2-methoxyphenyl) urea;

31. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(2-methylphenyl) urea;

32. N-(4-chloro-2-methylphenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}urea;

33. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(2-pyridyl)urea;

34. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(5-methyl-2-pyridyl)urea;

35. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(6-methyl-2-pyridyl)urea;

36. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(4-methoxyphenyl) urea;

37. N-(2, 4-difluorophenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl} urea;

38. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-propylurea;

39. N-(4-chloro-2-methylphenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}urea;

40. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(4-fluoro-2-methylphenyl)urea;

41. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(3-fluoro-2-methoxyphenyl)urea;

42. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(2-methylphenyl) urea;

43. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(2-methoxyphenyl) urea;

44. N-(5-bromo-6-methyl-2-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}urea;

45. N-(2, 6-dimethoxy-3-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}urea;

46. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(4-methoxyphenyl)urea;

47. N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-nitrophenyl}-N'-propylurea;

48. N-(2, 4-difluorophenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-nitrophenyl} urea;

49. N-{3. 5-dichloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2, 4-difluorophenyl) urea;

50. N-(2, 4-difluorophenyl)-N'-(2-fluoro-4-{[(6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl)]oxy}phenyl)urea;

51. N-(2-chloro-4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}phenyl)-N'-(2, 4-difluorophenyl)urea;

52. N-(2, 4-difluorophenyl)-N'-(4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}-

2, 5-dimethylphenyl)urea;

53. N-(4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}-2, 5-dimethylphenyl)-N'- (2-methoxyphenyl)urea;

54. N-(2-chloro-4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}phenyl)-N'-(2, 4-difluorophenyl)urea;

55. N-(2-chloro-4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}phenyl)-N'-(2-methoxyphenyl)urea;

56. N-(2, 4-difluorophenyl)-N'-(4-{[6-methoxy-7-(2-methoxyethoxy)-4- quinolyl]-oxy}-2, 3-dimethylphenyl)urea;

57. N-(4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}-2, 3-dimethylphenyl)-N'-(2- methoxyphenyl)urea;

58. N-(2, 4-difluorophenyl)-N'-(4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]-oxy}-2, 5-dimethylphenyl)urea;

59. N-(4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}-2, 5-dimethylphenyl)-N'- (2-methoxyphenyl)urea;

60. N-(4-{[7-(benziloxy)-6-methoxy-4-quinolyl]oxy}-2, 3-dimethylphenyl)-N'-(2-methoxyphenyl)urea;

61. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-(2, 4-difluorophenyl)-urea;

62. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea;

63. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-ethylurea;

64. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-isobutylurea;

65. N-butyl-N'-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}urea;

66. N-allyl-N'-{2-chloro-4-[(6, 7-dimethoxy-4-qunazolinyl)oxy]phenyl}urea;

67. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-pentylurea; and

68. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-(2-propinyl)urea.

[0030]

Examples of more preferred compounds according to the present invention include the following compounds:

13. N-{2-chloro-4-[(6, 7-dimethyl-4-quinolyl)oxy]phenyl}-N'-propylurea;

18. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2-methoxyphenyl) urea;

28. N-(5-chloro-2-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}urea;

37. N-(2, 4-difluorophenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}urea; and

62. N-{2-chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-propylurea.

[0031]

The compounds according to the present invention may form pharmaceutically acceptable salts thereof. Preferred examples of such salts include: alkali metal or alkaline earth metal salts such as sodium salts, potassium salts or calcium salts; hydrohalogenic acid salts such as hydrofluoride salts, hydrochloride salts, hydrobromide salts; or hydroiodide salts; inorganic acid salts such as nitric acid salts, perchloric acid salts, sulfuric acid salts, or phosphoric acid salts; lower alkylsulfonic acid such as methanesulfonic acid salts, trifluoromethanesulfonic acid salts, or ethanesulfonic acid salts, arylsulfonic acid salts such as benzenesulfonic acid salts or p-toluenesufonic acid salts; organic acid salts such as fumaric acid salts, succinic acid salts, citric acid salts, tartaric acid salts, oxalic acid salts, maleic acid salts, acetic acid salts, malic acid salts, latic acid salts, or ascorbic acid salts; and amino acid salts such as glycine salts, phenylalanine salts, glutamix acid salts, or aspartic acid salts.

[0032]

The compounds according to the present invention may form solvates (for example, hydrates).

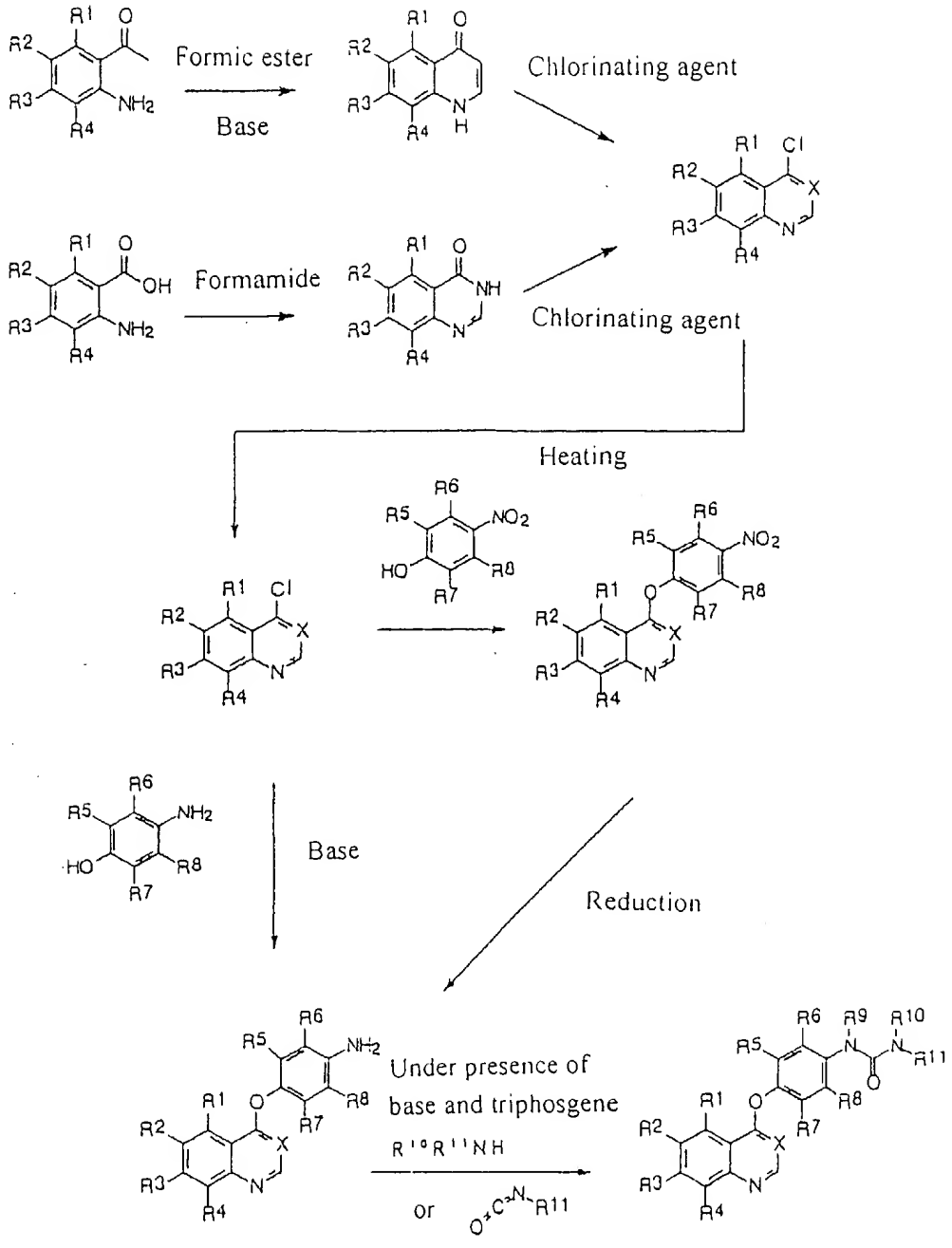
[0033]

Production of compounds

The compounds according to the present invention may be produced, for example, according to scheme 1 and scheme 2.

[0034]

[Chemical Formula 5]



Starting compounds necessary for the synthesis of the compounds according to the present invention may be commercially available, or alternatively may be produced

according to a conventional process. For example, a 4-chloroquinoline derivative may be synthesized by a conventional process as described in Org. Synth. Col. Vol. 3, 272 (1955), Acta Chim. Hung., 112, 241 (1983) or WO 98/47873. A 4-chloroquinazoline derivative may be synthesized by a conventional process as described in J. Am. Chem. Soc., 68 1299 (1946) or J. Am. Chem. Coc., 68, 1305 (1946).

[0035]

Next, 4-chloroquinoline derivative or a corresponding quinazoline derivative is allowed to act on nitrophenol in the presence of a suitable solvent or in the absence of a solvent to synthesize a 4-(nitrophenoxy) quinoline derivative or a corresponding quinazoline derivative which is then stirred in a suitable solvent, for example, N, N-dimethylformamide, in the presence of a catalyst, for example, palladium hydroxide-carbon or palladium-carbon, in a hydrogen atmosphere to give a 4-(aminophenoxy) quinoline derivative or a corresponding quinazoline derivative. Alternatively, a 4-chloroquinoline derivative or a corresponding quinazoline derivative may be allowed to act on aminophenol in the presence of a base, for example, sodium hydride, to give a 4-(aminophenoxy) quinoline derivative or a corresponding quinazoline derivative. Alternatively, the 4-(aminophenoxy) quinoline derivative or the corresponding quinazoline derivative may be reacted with an aldehyde or a ketone to produce an imine, followed by reduction, for example with sodiumboroncyanohydride to introduce a substituent into R^9.

[0036]

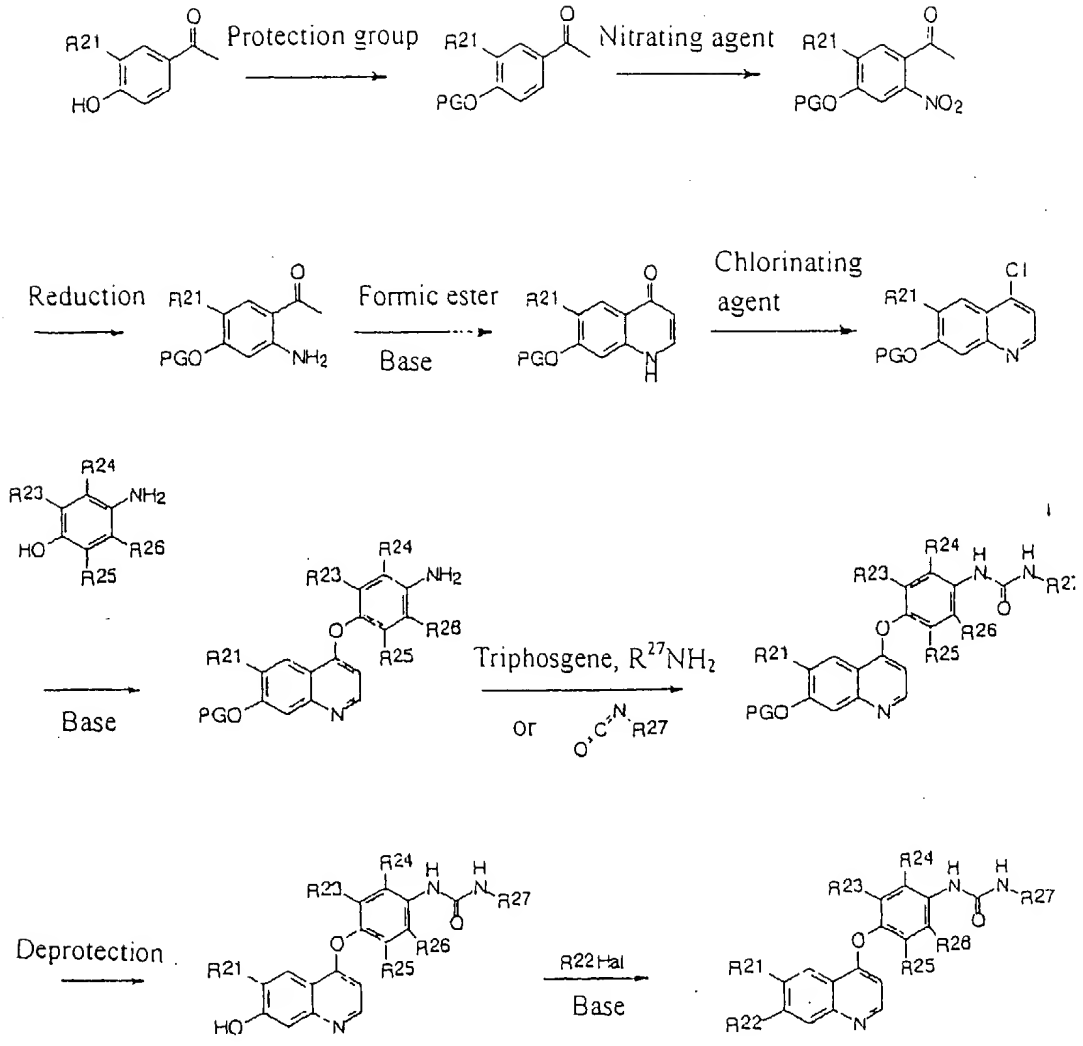
These derivatives may be synthesized by allowing an isocyanate derivative (O = C = N - R^{11}) to act on the derivative thus obtained according to a conventional method, or by treating the derivative with triphosgene and then allowing an aromatic amine or alkylamine ($R^{10}R^{11}NH$). The substituent of the urea portion (R^9 and R^{10}) may be synthesized by allowing an appropriate alkylating agent to act on the urea derivative wherein R^9 and R^{10} represent a hydrogen atom in the presence of a base.

[0037]

Further, for example, the derivative having a specific substituent at the 7-position of the quinoline ring may be produced according to the following scheme.

[0038]

[Chemical Formula 6]



A suitable substituent (for example, benzyl) may be allowed to act on a commercially available 4'-hydroxyacetophenone derivative to protect the hydroxyl group, followed by action of a nitrating agent (for example, nitric acid-acetic acid) to

introduce a nitro group. The nitro group may be then reduced to an amino group which is then reacted with a formic ester in the presence of a base to form a quinolone ring, followed by action of a chlorinating agent, for example, phosphorus oxychloride, to produce a 4-chloroquinoline derivative. The 4-chloroquinoline derivative thus obtained may be allowed to act on aminophenol in the presence of a base, for example, sodium hydride, to produce a 4-(aminophenoxy) quinoline derivative. The urea portion may be synthesized by allowing an isocyanate derivative ($O = C = N - R^{27}$) to act on the derivative thus obtained according to a conventional method, or by treating the derivative with triphosgene and then allowing an aromatic amine or alkylamine ($R^{27}NH_2$) to act on the treated derivative. Next, the protective group (PG) for the hydroxyl group at the 7-position of the quinoline ring may be removed, followed by action of an alkyl halide ($R^{22}Hal$) in the presence of a base, to produce a derivative wherein the 7-position is substituted by a specific substituent.

[0039]

Use of compounds/pharmaceutical composition

The compounds according to the present invention have inhibitory activity against tumor proliferation in vivo (see Pharmacological Test Example 3).

[0040]

Further, the compounds according to the present invention inhibit in vitro the activation of MAPK (mitogen-activated protein kinase) caused by stimulation of vascular endothelial cells with VEGF (vascular endothelial growth factor) (see Pharmacological Test Example 1). Upon the stimulation of vascular endothelial cells with VEGF, MAPK is activated by a signal transmission system downstream of the receptor, and, consequentily, an increase in phosphorylated MAPK is recognized (Abedi, H. and Zachary, I., J. Biol. Chem., 272, 15442-15451 (1997)). The activation of MAPK is known to play an important role in the growth of vascular endothelial cells in angiogenesis (Merenmies, J. et al., Cell Growth & Differ., 83-10 (1997)); and Ferrara, N. and Davis –Smyth, T., Endocr. Rev., 18, 4-25 (1997)). Therefore, the compounds according to the present invention have angiogenesis inhibitory activity.

[0041]

Angiogeneisis at pathologic sites is deeply involved mainly in diseasses, such as tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kaposi's sarcoma, and metastasis of solid tumors (Forkman, J. Nature Med. 1: 27-31 (1995); Bicknell, R., Harris, A. L. Curr. Opin. Ohcol. 8: 60-65 (1996)). Therefore, the compounds according to the present invention can be used in the treatment of diseases, such as tumor, diabeti retinophathy, chronic rheumatism, proriasis, atherosclerosis, and Kaposi's sarcoma, and metastasis of solid tumors.

[0042]

The compounds according to the present invention have no significant influence on cyromorphosis (see Pharmacological Test Example 2). Therefore, the compounds according to the present invention can be administered to living bodies with very excellent safety.

[0043]

According to another aspect of the present invention, there is provided a pharmaceutical composition comprising the compounds according to the present invention. The compounds according to the present invention may be used in the treatment of diseases, such as tumor, diabetic retinopathy, chronic rheumatism, psoriasis, atherosclerosis, and Kapsi's sarcoma, and mateastasis of solid tumors.

[0044]

The compounds according to the present invention can be administered to human and non-human animals orally or parenterally by administration routes, for example, intravenous administration, intramuscular administration, subcutaneous administration, recatal administration, or percutaneous administration. Therefore, the pharmaceutical composition comprising as an active ingredient the compound according to the present invention is formulated into suitable dosage forms according to the administration routes.

[0045]

Specifically, oral preparations include tablets, capsules, powders, granules, and syrups, and parental preparations include injections, suppositories, tapes, and ointments.

[0046]

These various preparations may be prepared by conventional methods, for example, with commonly used components, such as excipients, disintegrants, binders, lubricants, colorants, and diluents.

[0047]

Excipients include, for example, lactose, glucose, corn starch, sorbit, and crystalline cellulose. Disintegrants include, for example, starch, sodium alginate, gelatin powder, calcium carbonate, calcium citrate, and dextrin. Binders include, for example, dimethylcellulose, plyvinyl alcohol, plyvinyl ether, mehylcellulose, echylcellulose, gun arabic, gelatin, hydroxypropylcellulose, and polyvinyl pyrrolidone. Lubricants include, for example, talc, magnesium stearate, polyethylene glycol, and hydrogenated vegetable oils.

[0048]

In preparing injections, if necessary, for example, buffers, pH adjustors, stabilizers, tonicity agents, and preservatives may be added.

[0049]

The content of the compounds according to the present invention in the pharmaceutical composition according to the present invention may vary according to the dosage form. In general, however, the contents is 0.5 to 50% by weight, preferably 1 to 20 % by weight, based on the whole composition.

[0050]

The dose may be appropriately determined in consideration of, for example, the age, weight, sex, difference in diseases, and severity of condition of patients, and the preparation may be administered, for example, in an amount of 0.1 to 100 mg/kg, preferably 1 to 50 mg/kg. This dose is administered at a time daily or divided doses of several times daily.

[0051]

[Examples]

The present invention will be described with reference to the following example, though it is not limited to these examples only.

[0052]

Production Example 1: 2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]aniline

Sodium hydride (60 wt%, 0.72 g) was added to dimethyl sulfoxide (10 ml). The mixture was stirred at 50℃ for 30 min and was then cooled to room temperature. 4-Amino-3-chlorophenol hydrochloride (1.61 g) was added to the cooled mixture, and the mixture was stirred at room temperature for 10 min. Next, 4-chloro-6, 7-dimethoxyquinoline (1.00 g) was added thereto, and the mixture was stirred at 100℃ overnight. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and methanol was added to the residue. The precipitated crystal was collected by suction filtration to give 0.89 g (yield 60%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 4.05 (s, 3H), 4.08 (s, 2H), 6.44 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6,93-6.96 (m, 1H), 7.15 (d, J = 2.7 Hz, 1H), 7.41 (s, 1H), 7.54 (s, 1H), 8.48 (d, J = 5.1 Hz, 1H)

[0053]

Production Example 2: 4- [(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylaniline

Sodium hydride (60 wt%, 0.72 g) was added to dmethyl sulfoxide (10 ml). The mixture was stirred at 50℃ for 30 min and was then cooled to room temperature. 4-Amino-2, 3-dimehylphenol hydrochloride (1.55 g) was added to the cooled mixture, and the mixture was stirred at room temperature for 10 min. Next, 4-chloro-6, 7-dimethoxyquinoline (1.00 g) was added thereto, and the mixture was stirred at 100℃ overnight. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and methanol was added to the residue. The precipitated crystal was collected by suction filtration to give 0.94 g (yield 65%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.07 (s, 3H), 2.15 (s, 3H), 3.62 (s, 2H), 4.05

(s, 3H), 4.07 (s, 3H), 6.25 (d, J = 5.4 Hz, 1H), 6.64 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 7.42 (s, 1H), 7.64 (s, 1H), 8.42 (d, J = 5.4 Hz, 1H)

[0054]

Production Example 3: 4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylaniline

Sodium hydride (60 wt%, 0.36 g) was added to dimethyl sulfoxide (10 ml), and the mixture was stirred at 50℃ for 30 min and was then cooled to room temperature. 4-Amino-2, 5-dimethylphenol (1.23 g) was added to the cooled mixture, and the mixure was stirred at room temperature for 10 min. Next, 4-chloro-6, 7-dimethoxyquinoline (1.00 g) was added thereto, and the mixture was stirred at 100℃ overnight. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/acetone (1/1) to give the title compound.

[0055]

Production Example 4: 3, 5-Dichloro-4-[(6,7-dimetoxy-4-quinolyl)oxy]aniline

Sodium hydride (60 wt%, 0.36 g) was added to dimethyl solfoxide (10 ml), and the mixture was stirred at 50℃ for 30 min and was then cooled to room temperature. 4-Amino-2, 6-dichlorophenol (1.59 g) was added to the cooled mixture, and the mixture was stirred at room temperature for 10 min. Next, 4-chloro-6, 7-dimethoxyquinoline (1.00 g) was added thereto, and the mixture was stirred at 100℃ overnight. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/acetone (1/1) to give 0.35 g (yield 22%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.84 (s, 2H), 4.05 (s, 3H), 4.08 (s, 3H), 6.28 (d, J = 5.4 Hz, 1H), 6.74 (s, 2H), 7.43 (s, 1H), 7.64 (s, 1H), 8.48 (d, J = 5.4 Hz, 1H)

[0056]

Production Example 5: 4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-nitroaniline

Sodium hydride (60 wt%, 0.54 g) was added to dimethyl sulfoxide (15 ml), and the mixture was stirred at 70℃ for 30 min and was then cooled to room temperature. 4-Amino-3-nitrophenol (2.07 g) was added to the cooled mixture, and the mixture was stirred at room temperature for 10 min. Next, 4-chloro-6, 7-dimethoxyquinoline (1.50 g) was added thereto, and the mixture was stirred at 100℃ for 4 hr. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/acetone (1/1) to give 0.53 g (yield 23%) of the title compound.

[0057]

Production Example 6: 1-[2-Amino-4-(benzyloxy)-5-methoxyphenyl]-1-ethanone

1-(4-Hydroxy-3-methoxyphenyl)-1-ethanone (20 g), potassium carbonate (18.3 g), tetra-n-butylammonium iodide (4.45 g), and benzyl bromide (17.3 ml) were dissolved in N, N-dimethylformamide (300 ml), and a reaction was allowed to proceed at 100℃ for one hr. The solvent was removed by distillation under the reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate. The ethyl acetate layer was dried over sodium sulfate. Next, the solvent was removed by distillation under the reduced pressure. The residue and fuming nitric acid (12.47 ml) were dissolved in acetic acid (120 ml), and a reaction was allowed to proceed at room temperature for 2 hr. The reaction solution was neutralized at 0℃ by the addition of an aqueous sodium hydroxide solution, followed by extraction with chloroform. The chloroform layer was then dried over sodium sulfate. Next, the solvent was removed by distillation under the reduced pressure. The residue was dissolved in ethanol (1160 ml) and water (120 ml) with heating. Ammonium chloride (19.2 g) and zinc (101.7 g) were added thereto. The mixture was heated under reflux for 3 hr. The reaction solution was filtered through Celite, followed by washing with

chloroform/methanol (3/1). The solvent was removed by distillation under the reduced pressure, and the residue was made alkaline with an aqueous sodium hydroxide solution, and the alkaline solution was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/ethyl acetate (10/1) to give 24.95 g (yield 77%) of the title compound (3 steps).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.51 (s, 3H), 3.84 (s, 3H), 5.14 (s, 2H), 6.12 (s, 2H), 7.15-7.62 (m, 7H)

[0058]

Production Example 7: 7-(Benzyloxy)-6-methoxy-1, 4-dihydro-4-quinolinone

1-[2-Amino-4-(benzyloxy)-5-methoxyphenyl]-1-ethanone (24.95 g) was dissolved in tetrahydrofuran (450 ml), and sodium methoxide (24.87 g) was added to the solution. The mixture was stirred at room temperature for one hr. Ethyl formate (37.07 ml) was then added thereto, and the mixture was stirred at room temperature for 2 hr. Water (150 ml) was then added thereto, and the mixture was stirred overnight. The reaction solution was adjusted to pH 4 by the addition of concentrated sulfuric acid at 0℃. Water was added thereto, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (10/1) to give 17.16 g (yield 66%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.84 (s, 3H), 5.19 (s, 2H), 5.97 (d, J = 7.1 Hz, 1H), 7.09 (s, 1H), 7.28-7.51 (m, 6H), 7.78 (d, J = 7.3 Hz, 1H), 11.50-11.75 (br, 1H)

[0059]

Production Example 8: 7-(benzyloxy)-4-chloro-6-methoxyquinoline

Phsphrus oxychloride (14.19 ml) was added to 7-(benzyloxy)-6-methoxy-1, 4-dihydro-4-quinolinone (17.16 g), and the mixture was heated under reflux for one hr. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in chloroform, and the solution was made alkaline by the addition of an aqueous

sodium hydroxide solution, followed by extraction with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/acetone (10/1) to give 3.82 g (yield 21%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.06 (s, 3H), 5.32 (s, 2H), 7.30-7.55 (m, 8H), 8.56 (d, J = 4.9 Hz, 1H)

[0060]

Production Example 9: 4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}2, 5-dimethylaniline

Sodium hydride (60 wt%, 1.17 g) was added to dimethyl sulfoxide (25 ml), and the mixture was stirred at 60℃ for 30 min and was then cooled to room temperature. Next, 4-amino-2, 5-dimethylphenol (4.00 g) was added thereto, and the mixture was stirred at room temperature for 10 min. 7-(Benzyloxy)-4-chloro-6-methoxyquinoline (4.36 g) was then added thereto. The mixture was stirred for 22 hr before water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and methanol was added to the residue to prepare a suspension. The precipitated crystal was collected by suction filtration to give 3.04 g (yield 52%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.04 (s, 3H), 2.16 (s, 3H), 3.58 (s, 2H), 4.06 (s, 3H), 5.32 (s, 2H), 6.28 (d, J = 5.1 Hz, 1H), 6.61 (s, 1H), 6.81 (s, 1H), 7.28-7.42 (m, 3H), 7.44 (s, 1H), 7.49-7.54 (m, 2H), 7.63 (s, 1H), 8.39 (d, J = 5, 1 Hz, 1H)

Mass analysis, found (ESI = MS, m/z): 401 ($M^+ + 1$)

[0061]

Production Example 10: N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2,5-dimethylphenyl)-N'-(2, 4-difluorophenyl)urea

4-{[7-(benzyloxy)-6-methoxy-4-quinolyl]oxy}-2, 5-dimethylaniline (300 mg) was dissolved in chloroform (5 ml). 2, 4-Difluorophenyl isocyanate (200 µl) was then added to the solution, and the mixture was purified by 70℃ overnight. The reaction

solution was purified by chromatography on silica gel by development with chloroform/acetone (75/25) to give 368 mg (yield 88%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.26 (s, 3H), 4.06 (s, 3H), 5.33 (s, 2H), 6.29 (d, J = 5.1 Hz, 1H), 6.42 (s, 1H), 6.76-6.93 (m, 3H), 6.70 (s, 3H), 7.30-7.54 (m, 7H), 7.60 (s, 1H), 8.04-8.12 (m, 1H), 8.44 (d, J = 5.4 Hz, 1H)

[0062]

Production Example 11: N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2, 5-dimethylphenyl)-N'-(2-methoxyphenyl)urea

4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2, 5-dimethylaniline (300 mg) was dissolved in chloroform (5 ml). 2-Methoxyphenyl isocyanate (0.24 ml) was then added to the solution, and the mixture was stirred at 70℃ overnight. The reaction solution was purified by chromatography on silica gel by development with chloroform/acetone (75/25) to give 365 mg (yield 89%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.28 (s, 3H), 3.83 (s, 3H), 4.07 (s, 3H), 5.33 (s, 2H), 6.26 (s, 3H), 6.29 (d, J = 5.4 Hz, 1H), 6.86-7.06 (m, 4H), 7.12 (s, 1H), 7.30-7.41 (m, 3H), 7.46 (s, 1H), 7.50-7.56 (m, 3H), 7.61 (s, 1H), 8.11-8.16 (m, 1H), 8.43 (d, J = 5.4 Hz, 1H)

[0063]

Production Example 12: 4-{[7-(benzyloxy)-6-methoxy-4-quinolyl]oxy}-2-chloroanilyne

Sodium hydride (60 wt%, 320 mg) was added to dimethyl sulfoxide (3.6 ml), and the mixture was stirred at 60℃ for 30 min and was then cooled to room temperature. Next, 4-amino-3-chlorophenol hydrochloride (720 mg) was added thereto, and the mixture was stirred at room temperature for 10 min. 7-(Benzyloxy)-4-chloro-6-methoxyquinoline (600 mg) was then added thereto, and the mixture was stirred at 150℃ for 22 hr. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and methanol was added to the residue to prepare a suspension. The precipitated crystal was collected by suction filtration to give 533 mg (yield 66%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 4.08 (s, 2H), 5.32 (s, 2H), 6.42 (d, J = 5.1 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 6.93 (dd, J = 2.4 Hz, 8.1 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.29-7.42 (m, 3H), 7.44 (s, 1H), 7.49-7.53 (m, 2H), 7.55 (s, 1H), 8.45 (d, J = 5.3 Hz, 1H)

Mass analysis, found (ESI - MS, m/z): 497 (M^+ + 1)

[0064]

Production Example 13: N-(4-{[7-(benzyloxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-(2, 4-difluorophenyl)urea

4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2-chloroaniline (260 mg) was dissolved in chloroform (10 ml). 2, 4-Difluorophenyl isocyanate (198 mg) was then added to the solution, and the mixture was stirred at room temperature for 2 hr. The reaction solution was purified by chromatography on silica gel by development with chloroform/acetone (10/1) to give 337 mg (yield 94 %) of the title compound.

[0065]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.04 (s, 3H), 5.32 (s, 2H), 6.49 (d, J = 5.1 Hz, 1H), 6.86-6.96 (m, 3H), 7.10-7.17 (m, 2H), 7.22-7.28 (m, 1H), 7.28-7.41 (m, 3H), 7.45-7.53 (m, 4H), 7.96-8.04 (m, 1H), 8.27 (d, J = 9.0 Hz, 1H), 8.49 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI - MS, m/z): 562, 564 (M^+ + 1)

[0066]

Production Example 14: N-{2-chloro-4-[(7-hidroxy-6-methoxy-4-quinolyl)oxy]phenyl}-N'-(2, 4-difluorophenyl)urea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2-chlorophenyl)-N'-(2, 4-difluorophenyl)urea (215 mg) was dissolved dimethylformamide (11 ml). Palladium-carbon (215 mg) was added to the solution, and the mixture was stirred in a hydrogen atmosphere at room temperature overnight. Ethyl acetate (30 ml) was added to the reaction solution, and the mixture was then filtered through Celite. The solvent was removed by distillation under the reduced pressure to give 174 mg (yield 96%) of the title compound.

[0067]

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.94 (s, 3H), 6.47 (d, J = 5.1 Hz, 1H),

7.01-7.11 (m, 1H), 7.18-7.36 (m, 3H), 7.44-7.52 (m, 2H), 7.95 (s, 1H), 7.98-8.13 (m, 1H), 8.23 (d, J = 9.5 Hz, 1H), 6.50 (d, J = 5.1 Hz, 1H), 8.81 (s, 1H), 9.31 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 472 ($M^+ + 1$)

[0068]

Production Example 15: 4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2, 3-dimethylaniline

Sodium hydride (60 wt%, 0.32 g) was added to dimethyl solfoxide (6 ml), and the mixture was stirred at room temperature for 30 min. 4-Amino-2, 3-dimethylphenol (1.10 g) was then added thereto, and the mixture was stirred at room temperature for 10 min. Next, 7-(bezyloxy)-4-chloro-6-methoxyquinoline (1.20 g) was added thereto, and the mixture was stirred at 110 ℃ for 6 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/acetone (6/1) to give 0.78 g (yield 49%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.87 (s, 3H), 1.96 (s, 3H), 3.97 (s, 3H), 4.78 (s, 2H), 5.23 (s, 2H), 6.12 (d, J = 5, 3 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 7.27-7.51 (m, 7H), 8.31 (d, J = 5.3 Hz, 1H)

[0069]

Production Example 16: N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2, 3-dimethylphenyl)-N'-(2, 4-difluorophenyl)urea

4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2, 3-dimethylaniline (260 mg) was dissolved in N, N-dimethylformamide (5 ml). 2, 4-Difluorophenyl isocyanate (121 mg) was then added to the solution, and a reaction was allowed to proceed at room temperature overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was washed with methanol and was collected by filtration to give 219 mg (yield 61%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.99 (s, 3H), 2.17 (s, 3H), 3.90 (s, 3H), 5.24 (s, 2H), 6.18 (d, J = 5.1 Hz, 1H), 6.95-6.98 (m, 2H), 7-25-7.63 (m, 9H) 8.05-8.08

(m, 1H), 8.34-8.36 (m, 2H), 8.79 (s, 1H)

[0070]

Production Example 17: 7-(Benzyloxy)-4-(3-fluoro-4-nitrophenoxy)-6-methoxyquinoline

7-(Benzyloxy)-4-chloro-6-methoxyquinoline (300mg) and 3-fluoro-4-nitrophenol (785 mg) were dissolved in chlorobenzene (3 ml), and the solution was stirred at 130℃ for 5 hr. Chloroform and an aqueous sodium hydroxide solution was added to the reaction solution, and the mixture was stirred for one hr. The reaction solution was extracted with chloroform, and the chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with hexane/ethyl (1/1) to give 197 mg (yield 47%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.83 (s, 3H), 5.25 (s, 2H), 6,91 (d, J = 5.1 Hz, 1H), 7.29-7-50 (m, 9H), 8.18-8.23 (m, 1H), 8.56 (d, J = 5.1 Hz, 1H)

[0071]

Production Example 18: 4-(4-amino-3-fluorophenoxy)-6-methoxy-7-quinolinol

7-(Benzyloxy)-4-(3-fluoro-4-nitrophenoxy)-6-methoxyquinoline (190 mg) was dissolved in N, N-dimethylformamide (5 ml) and triethylamine (1 ml). Palladium hydroxide (40 mg) was added to the solution, and the mixture was stirred in a hydrogen atmosphere at room temperature overnight. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (20/1) to give 75 mg (yield 56%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.87 (s, 3H), 5.11 (s, 2H), 6.29 (d, J = 5.1 Hz, 1H), 6.77-6.80 (m, 2H), 6.93-6.99 (m, 1H), 7.19 (s, 1H), 7.40 (s, 1H), 8.31 (d, J = 5.1 Hz, 1H), 10.03 (s, 1H)

[0072]

Production Example 19: N-(2, 4-Difluorophenyl)-N'-{2-fluoro-4-[(7-hydroxy-6-methoxy- 4-quinolyl)oxy]phenyl}urea

4-(4-Amino-3-fluorophenoxy)-6-methoxy-7-quinolinol (70 mg) was dissolved

in chloroform (1.5 ml) and N, N-dimethylformamide (1 ml). 2, 4-Difluorophenyl isocyanate (43 mg) was then added to the solution, and a reaction was allowed to proceed at room temperature for 3 hr. Methanol was added to the reaction solution. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (20/1) to quantitatively give the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.94 (s, 3H), 6.47 (d, J = 5.1 Hz, 1H), 7.04-7.10 (m, 2H), 7.28-7.34 (m, 2H), 7.47 (s, 1H), 8.05-8.15 (m, 2H), 8.30 (s, 1H), 8.43 (d, J = 5.1 Hz, 1H), 8.97-9.03 (m, 2H), 10.10 (s, 1H)

[0073]

Production Example 20: 4-Chloro-6-methoxy-7-quinolinol

7-(Benzyloxy)-4-chloro-6-methoxyquinoline (100 mg), thioanisole (300 µl), and methanesulfonic acid (25 µl) were dissolved in trifluoromethanesulfonic acid (1 ml). The solution was stirred at room temperature for 30 min. The solvent was removed by distillation under the reduced pressure. The residue was made neutral by the addition of an aqueous sodium hydroxide solution, and hexane was added thereto to prepare a suspension. The crystal was collected by suction filtration to give 53 mg (yield 75%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.98 (s, 3H), 7.33 (s, 1H), 7.36 (s, 1H), 7.47 (d, J = 4.9 Hz, 1H), 8.54 (d, J = 4.9 Hz, 1H), 10.37 (br, 1H)

[0074]

Production Example 21: 4-Chloro-6-methoxy-7-(2-methoxyethoxy)quinoline

4-Chloro-6-methoxy-7-quinolinol (50 mg), potassioum carbonate (40 mg), tetra-n-butylammonium iodide (9 mg), and 2-bromoethyl methyl ether (40 mg) were dissolved in N, N-dimethylformamide (10 ml). The solution was stirred at 70℃ overnight. The solvent was removed by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, followed by extraction with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with

hexan/acetone/dichloromethane (6/2/1) to give 47 mg (yield 74%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.49 (s, 3H), 3.88-3.90 (m, 2H), 4.04 (s, 3H), 4.32-4.35 (m, 2H), 7.35 (d, J = 4.9 Hz, 1H), 7.40 (s, 1H), 7.43 (s, 1H), 8.57 (d, J = 4.9 Hz, 1H)

[0075]

Production Example 22: 2-Chloro-4-{[(6-methoxy-7-(2-methoxyethoxy)-4-quinoly)oxy]aniline

Sodium hydride (60 wt%, 153 mg) was added to dimethyl solfoxide (2 ml). The mixture was stirred at 60℃ for 30 min and was then cooled to room temperature. 4-Amino-3-chlorophenol hydrochloride (343 mg) was added thereto, and the mixture was stirred at room temperature for 10 min. Next, a solution of 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinoline (254 mg) in dimethyl sulfoxide (2 ml) was added to the reaction solution, and the mixture was stirred at 110℃ overnight. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone4 (7/3) to give the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.49 (s, 3H), 3.89-3.91 (m, 2H), 4.02 (s, 3H), 4.09 (s, 2H), 4.33-4.35 (m, 2H), 6.43 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.93-6.96 (m, 1H), 7.15 (d, J = 2.7 Hz, 1H), 7.41 (s, 1H), 7.52 (s, 1H), 8.47 (d, J = 5.1 Hz, 1H)

[0076]

Production Example 23: 2-Chloro-4-[(6, 7-dimetoxy-4-quinazolinyl)oxy]aniline

Sodium hydride (60 wt%, 5.80 g) was added to dimethyl sulfoxide (40 ml). The mixture was stirred at 60℃ for 30 min and was then cooled to room temperature. Next, 4-amino-3-chlorophenol hydrochloride (13.05 g) was added thereto. The mixture was stirred at room temperature for 10 min. 4-Chloro-6, 7-dimethoxyquinazoline (8.14 g), which is a chloroquinazoline derivative synthesized

by a conventional method as described, for example, in J. Am. Chem. Soc., 68, 1299 (1946) or J. Am. Chem. Soc., 68, 1305 (1946), was then added thereto. The mixture was stirred at 110℃ for 30 min. Water was then added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and methanol was added to the residue to prepare a suspension. The precipitated crystal was collected by suction filtration to give 9.13 g (yield 76%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.05-4.08 (m, 8H), 6.85 (d, J = 8.5 Hz, 1H), 7.00 (dd, J = 2.7 Hz, 8.8 Hz, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.32 (s, 1H), 7.52 (s, 1H), 8.64 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 332 ($M^+ + 1$)

[0077]

Production Example 24: N-Benzyl-N-(2, 4-difluorophenyl)amine

Magnesium sulfate (5.59 g) and a minor amount of acetic acid were added to a solution of 2, 4-difluoroaniline (2.37 ml) and bezaldehyde (2.36 ml) in methanol (46 ml). The mixture was stirred at room temperature for 45 min. Sodium boron hydride (2.64 g) was added thereto under ice cooling, and the mixture was stirred at room temperature for one hr. The solvent was removed by distillation under the reduced pressure. Water and ethyl acetate were added to the residue. The mixture was stirred and was filtered through Celite. The organic layer was extracted with ethyl acetate and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with hexane/acetone (30/1) to give 3.04 g (yield 60%) of the title compound.

[0078]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.34 (s, 2H), 6.56-6.82 (m, 3H), 7.25-7.38 (m, 5H)

[0079]

Example 1: N-(2, 4-Difluorobenzyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophynyl}urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (5.0 ml) and triethylamine (1.0 ml) with heating. A solution of triphosgene (103 mg) in dichloromethane (1.0 ml) was then added to the solution, and the mixture was heated under reflux for 3 min. Next, 2, 4-difluorobenzylamine (54 mg) was added thereto, and the mixture was heated under reflux for additional 5 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 123 mg (yield 80%) of the title compound.

[0080]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.02 (s, 3H), 4.03 (s, 3H), 4.47 (d, J = 5.9 Hz, 2H), 5.78-5.90 (m, 1H), 6.46 (d, J = 5.4 Hz, 1H), 6.74-6.99 (m, 4H), 7.03-7.14 (m, 1H), 7.35-7.44 (m, 2H), 7.50 (s, 1H), 8.16 (t, J = 9.0 Hz, 1H), 8.47 (d, J = 5.1 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 483 (M^+)

[0081]

Example 2: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(2-fluoroethyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (10 ml) and triethylamine (0.5 ml) with heating. A solution of triphosgene (47 mg) in dichloromethane (1.0 ml) was then added to the solution, and the mixture was heated under reflux for 5 min. Next, 2-fluoroethylamine hydrochloride (42 mg) was added thereto, and the mixture was heated under reflux for additional 8 hr. A saturated aqueous sodium hydrogencarbnate solution was added to the reaction solution, followed by extraction with ethyl acetate. The ethyl acetate layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with

chloroform/acetone (2/1) to give 93 mg (yield 72%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.40 (m, 1H), 3.47 (m, 1H), 3.93 (s, 3H), 3.95 (s, 3H), 4.42 (t, J = 4.9 Hz, 1H), 4.54 (t, J = 4.9 Hz, 1H), 6.51 (d, J = 5.4 Hz, 1H), 6.88 (m, 1H), 7.05 (m, 1H), 7.28 (dd, J = 2.7 Hz, J = 11.7 Hz, 1H), 7.40 (s, 1H), 7.49 (s, 1H), 8.21 (m, 1H), 8.47 (br, 1H), 8.48 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI - MS, m/z): 404 (M^+ + 1)

[0082]

Example 3: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(2-pyridylmethyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (5 ml) and triethylamine (1 ml). A solution of triphosgene (104 mg) in dichloromethane was then added to the solution, and the mixture was refluxed for 5 min. Next, 2-(aminomethyl)pyridine (40 µl) was added thereto, and the mixture was heated under reflux for 2 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) and chloroform (2 ml) were added to the reaction solution. The mixture was supported on diatomaceous earth, followed by extraction with chloroform. The solvent was removed distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (8/1) to give 126 mg (yield 88%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.07 (s, 3H), 4.09 (s, 3H), 4.61 (d, J = 5.4 Hz, 2H), 6.40-6.50 (br, 1H), 6.61 (d, J = 5.9 Hz, 1H), 6.92-7.01 (m, 2H), 7.21-7.25 (m, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.56 (s, 1H), 7.68-7.78 (m, 2H), 7.75 (s, 1H), 8.27-8.34 (m, 1H), 8.49 (d, J = 6.1 Hz, 1H), 8.55 (d, J = 4 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 448 (M^+)

[0083]

Example 4: N-Allyl-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (5 ml) and trithylamine (1 ml), and a solution of triphsgene (104 mg) in dichloromethane was then added to the solution. The mixture was heated under reflux for 5 min. Next, allylamine (22 mg) was added to the reaction solution, and the

mixture was heated under reflux for additional 4 hr. A saturated aqueous sodium hydrogencarbonate solution (1 ml) and chloroform (2 ml) were added to the reaction solution, and the mixture was supported on diatomaceous earth, followed by extraction with chloroform. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 125 mg (yield 98%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.91-3.96 (m, 2H), 4.06 (s, 3H), 4.09 (s, 3H), 5.14-5.20 (m, 1H), 5.26-5.33 (m, 1H), 5.58-5.66 (br, 1H), 5.86-5.98 (m, 1H), 6.56 (d, J = 5.9 Hz, 1H), 6.88-7.01 (m, 2H), 7.23 (s, 1H), 7.55 (s, 1H), 7.66 (s, 1H), 8.26-8.33 (m, 1H), 8.47 (d, J = 59 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 397 (M^+)

[0084]

Example 5: N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-propylurea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (10 ml) and triethylamine (2 ml), and a solution of triphosgene (104 mg) in dichloromethane was then added to the solution. The mixture was heated under reflux for 5 min. Next, propylamine (29 mg) was added, and the mixture was heated under reflux for 40 min. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (10/1) to give 89 mg (yield 71%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.97 (t, J = 7.6 Hz, 3H), 1.55-1.64 (m, 2H), 3.24-3.29 (m, 2H), 4.05 (s, 3H), 4.06 (s, 3H), 5.11 (t, J = 5.4 Hz, 1H), 6.51 (d, J = 5.4 Hz, 1H), 6.74-6.76 (m, 1H), 6.91-6.99 (m, 2H), 7.47 (s, 1H), 7.52 (s, 1H), 8.18-8.23 (m, 1H), 8.49 (d, J = 5.6 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 399 (M^+)

[0085]

Example 6: N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'(4-fluorobutyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (6 ml) and triethylamine (1.0 ml) with heating, and a solution of triphosgene (104 mg) in dichloromethane (1.0 ml) was then added to the solution. The mixture was heated under reflux for 5 min. Next, 4-fluorobutylamine hydrochloride (55 mg) was added to the reaction solution, and the mixture was heated under reflux for additional 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 80 mg (yield 55%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.66-1.87 (m, 4H), 3.33-3.40 (m, 2H), 4.04 (s, 3H), 4.05 (s, 3H), 4,44 (t, J = 5.6 Hz, 1H), 4.56 (t, J = 5.7 Hz, 1H), 4.90 (t, J = 5.7 Hz, 1H), 6.48-6.52 (m, 2H), 6.93-7.02 (m, 2H), 7.42 (s, 1H), 7.51 (s, 1H), 8.15 (t, J = 8.9 Hz, 1H), 8.50 (d, J = 5.1 Hz, 1H)

Mass analysis, found (FD - MS, m/z): 431 (M^+)

[0086]

Example 7: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(2-propynyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (150 mg) was dissolved in chloroform (10 ml) and triethylamine (2 ml), and a solution of triphosgene (156 mg) in dichloromethane was added to the solution. The mixture was heated under reflux for 10 min. Next, propargylamine (53 mg) was added, and the mixture was heated under reflux for additional 30 min. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by

chromatography on silica gel by development with chloroform/acetone (2/1) to give 164 mg (yield 87%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.49-2.51 (m, 1H), 3.90-3.95 (m, 8H), 6.52 (d, J = 5.1 Hz, 1H), 6.89-6.92 (m, 1H), 7.04-7.06 (m, 1H), 7.26-7.29 (m, 1H), 7.39 (s, 1H), 7.49 (s, 1H), 8.16-8.20 (m, 1H), 8.46-8.49 (m, 2H)

[0087]

Example 8: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-ethylurea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (8 ml) and triethylamine (1.0 ml) with heating, and a solution of triphosgene (47 mg) in toluene (1.0 ml) was then added to the solution. The mixture was heated under reflux for 5 min. Next, ethylamine hydrochloride (60 mg) was added to the reaction solution, and the mixture was heated under reflux for additional 5 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrouos sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 70 mg (yield 53%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.21 (t, J = 7.3 Hz, 3H), 3.34 (m, 2H), 4.06 (s, 3H), 4.08 (s, 3H), 5.64 (br, 1H), 6.55 (d, J = 5.6 Hz, 1H), 6.89 (dd, J = 2.7 Hz, J = 11.2 Hz, 1H), 6.97 (m, 1H), 7.26 (br, 1H), 7.54 (s, 1H), 7.62 (s, 1H), 8.28 (t, J = 9.0 Hz, 1H), 8.47 (d, J = 5.6 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 386 (M^+ + 1)

[0088]

Example 9: N-Butyl-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-fluorophynyl}urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in toluene (8 ml) and triethylamine (1.0 ml) with heating, and a solution of triphosgene (47 mg) in toluene (1.0 ml) was then added to the solution. The mixture was heated under reflux for 5 min. Next, butylamine (80 mg) was added to the reaction solution, and the mixture was heated under reflux for additional 5 hr. A saturated aqueous sodium

hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 117 mg (yield 81%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.94 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.55 (m, 2H), 3.29 (dd, J = 7.1 Hz, J = 12.9 Hz, 2H), 4.06 (s, 3H), 4.09 (s, 3H), 5.72 (br, 1H), 6.56 (d, J = 5.9 Hz, 1H), 6. 88 (dd, J = 2.7 Hz, J = 11.2 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 7.33 (s, 1H), 7.55 (s, 1H), 7.65 (s, 1H), 8.30 (t, J = 9.0 Hz, 1H), 8.46 (d, J = 5.9 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 414 (M^+ + 1)

[0089]

Example 10: N-(sec-Butyl)-N'-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2- fluorophenyl}urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (104 mg) in dichloromethane was then added to the solution. The mixture was heated under reflux for 5 min. Next, sec-butylamine (48 µl) was added to the reaction solution. The mixture was heated under reflux for 10 min. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (8/2) to give 117 mg (yield 89%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.95 (t, J = 7.6 Hz, 3H), 1.18 (d, J = 6.6 Hz, 3H), 1.47-1.55 (m, 2H), 3.79-3.89 (m, 1H), 4.04 (s, 6H), 5.28 (d, J = 8.1 Hz, 1H), 6.48 (d, J = 5.4 Hz, 1H), 6.89-6.98 (m, 2H),7.08 (d, J = 2.7 Hz, 1H), 7.42 (s, 1H), 7.51 (s, 1H), 8.20-8.24 (m, J = 9.0 Hz, 1H), 8.48 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 414 (M^+ + 1)

[0090]

Example 11: N-{4-[(6, 7-Dimethosy-4-quinolyl)oxy]-2-fluorophenyl}- N'-isobutylurea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (104 mg) in in dichloromethane was then added to the solution. The mixture was heated under reflux

for 5 min. Next, isobutylamine (50 μl) was added to the reaction solution, and the mixture was heated under reflux for 10 min. The reaction solution was purified by chromatography on silica gel by development with chloroform/acetone (4/1). Thus, the title compound was quantitatively obtained.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.94 (d, J = 6.6 Hz, 6H), 1.77-1.84 (m, 1H), 3.10-3.13 (m, 2H), 4.03 (s, 3H), 4.03 (s, 3H), 5.58 (t, J = 5.4 Hz, 1H), 6.47 (d, J = 5.4 Hz, H), 6.88-6.97 (m, 2H), 7.18 (s, 1H), 7.41 (s, 1H), 7.50 (s, 1H), 8.18-8.23 (m, 1H), 8.48 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 414 (M^+ + 1)

[0091]

Example 12: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluorophenyl}-N'-(1, 2-dimethylpropyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-fluoroaniline (100 mg) was dissolved in chloroform (5 ml) and triethylamine (1 ml), and a solution of triphosgene (47 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 1, 2-dimethylpropylamine (55 μl) was added to the reaction solution, and the mixture was stirred at room temperature for 10 min. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 89 mg (yield 65%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.93 (d, J = 2.2 Hz, 3H), 0.95 (d, J = 2.4 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.72-1.80 (m, 1H), 3.76-3.84 (m, 1H), 4.04 (s, 3H), 4.05 (s, 3H), 4.91 (d, J = 8.5 Hz, 1H), 6.48 (d, J = 5.4 Hz, 1H), 6.74 (d, J = 2.9 Hz, 1H), 6.91-6.98 (m, 2H), 7.42 (s, 1H), 7.51 (s, 1H), 8.18-8.23 (m, 1H), 8.49 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 428 (M^+ + 1)

[0092]

Example 13: N-{2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-propylurea

2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]aniline (100 mg) was dissolved in chloroform (7.5 ml) and triethylamine (1 ml), and a solution of triphosgene (99 mg) in chloroform was then added to the solution. The mixture was heated under reflux for 5 min.

Next, n-propylamine (21 mg) was added to the reaction solution, and the mixture was heated under reflux for additional 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was supported on diatomaceous earth, followed by extraction with chloroform. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (8/1) to give 145 mg (yield 100%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.00 (t, J = 7.3 Hz, 3H), 1.58-1.65 (m, 2H), 3.24-3.31 (m, 2H), 4.04 (s, 3H), 4.05 (s, 3H), 4.91-4.97 (br, 1H), 6.48 (d, J = 5.1 Hz, 1H), 6.77 (s, 1H), 7.09-7.13 (m, 1H), 7.21 (d, J = 2.7 Hz, 1H), 7.43 (s, 1H), 7.52 (s, 1H), 8.25-8.30 (m, 1H), 8.50 (d, J = 5.1 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 415, 417 (M^+)

[0093]

Example 14: N-{2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'- (4-fluoro-2-methylphenyl)urea

2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 4-fluoro-2-methylaniline (126 µl) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 142 mg (yield 79%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.37 (s, 3H), 4.04 (s, 3H), 4.04 (s, 3H), 6.31 (s, 1H), 6.47 (d, J = 5.1 Hz, 1H), 6.97-7.06 (m, 3H), 7.11-7.14 (m, 1H), 7.19 (d, J = 2.7 Hz, 1H), 7.41-7.44 (m, 2H), 7.50 (s, 1H), 8.35 (d, J = 9.0 Hz, 1H), 8.50 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 482, 484 ($M^+ + 1$)

[0094]

Example 15: N-(5-Bromo-6-methyl-2-phyridyl)-N'-{2-chloro-4-[(6, 7-dimethoxy-4-

quinolyl)oxy]phynyl}urea

2-Chloro-4[(6, 7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 6-amino-3-bromo-2-methylpyridine (208 mg) was added at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 155 mg (yield 77%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.69 (s, 3H), 4.06 (s, 6H), 6.53 (d, J = 5.4 Hz, 1H), 6.56 (d, J = 8.5 Hz, 1H), 7.14-7.17 (m, 1H), 7.30 (d, J = 2.7 Hz, 1H), 7.44 (s, 1H), 7.53 (s, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.93 (s, 1H), 8.49 (d, J = 9.0 Hz, 1H), 8.52 (d, J = 5.4 Hz, 1H), 11,92 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 543, 545, 547 (M^+ + 1)

[0095]

Example 16: N-{2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(5-chloro-2-pyridyl)urea

2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-amino-5-chloropyridine (143 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 148 mg (yield 82%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.06 (s, 3H), 4.06 (s, 3H), 6.53 (d, J = 5.1 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 7.14-7.17 (m, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.44 (s, 1H), 7.53 (s, 1H), 7.64-7.67 (m, 1H), 8.28 (d, J = 2.7 Hz, 1H), 8.50-8.53 (m, 2H), 8.92 (s, 1H), 12.11 (brs, 1H)

Mass analysis, found (ESI-MS, m/z) 485, 487, 489: $(M^+ + 1)$

[0096]

Example 17: N-(5-Bromo-2-pyridyl)-N'-{2-chloro-4-[(6, 7-dimethoxy-4-quinolyl) oxy]phenyl}urea

2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-amino-5-bromopyridine (192 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 108 mg (yield 55%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.06 (s, 3H), 4.06 (s, 3H), 6.53 (d, J = 5.1 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 7.14-7.18 (m, 1H), 7.30 (d, J = 2.7 Hz, 1H), 7.45 (s, 1H), 7.53 (s, 1H), 7.77-7.80 (m, 1H), 8.15 (s, 1H), 8.39 (d, J = 2.4 Hz, 1H), 8.50 (d, J = 9.0 Hz, 1H), 8.52 (d, J = 5.4 Hz, 1H), 12.09 (brs, 1H)

Mass analysis, found (ESI-MS, m/z): 529, 531, 533 $(M^+ + 1)$

[0097]

Example 18: N-{2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phynyl}-N'-(2-methoxyphenyl)urea

2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]aniline (100 mg) was dissolved in chloroform (10 ml), and 2-methoxyphenyl isocyanate (54 mg) was added to the solution. The mixture was stirred at 60℃ overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (6/4) to give 111 mg (yield 77%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.85 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 6.50 (d, J = 5.1 Hz, 1H), 6.90-7.15 (m, 4H), 7.23 (d, J = 2.7 Hz, 1H), 7.35 (s, 1H), 7.36 (s, 1H), 7.44 (s, 1H), 7.52 (s, 1H), 8.05-8.07 (m, 1H), 8.34 (d, J = 9.0 Hz, 1H), 8.52 (d, J =

5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 480, 482 ($M^+ + 1$)

[0098]

Example 19: N-{2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2-methylphenyl)urea

2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml), and o-toluyl isocyanate (59 mg) was added to the solution. The mixture was stirred at room temperature overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution to precipitate a crystal. The crystal was collected by filtration to give 59 mg (yield 34%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.38 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 6.22 (s, 1H), 6.47 (d, J = 5.1 Hz, 1H), 7.01 (s, 1H), 7.11-7.14 (m, 1H), 7.18 (d, J = 2.7 Hz, 1H), 7.25-7.35 (m, 3H), 7.42 (s, 1H), 7.46 (d, J = 6.8 Hz, 1H), 7.50 (s, 1H), 8.37 (d, J = 8.8 Hz, 1H), 8.50 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 464, 466 ($M^+ + 1$)

[0099]

Example 20: N-{2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'- (5-methyl-2-pyridyl)urea

2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-amino-5-picoline (120 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanols was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 119 mg (yield 69%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.31 (s, 3H), 4.06 (s, 6H), 6.53 (d, J = 5.4 Hz,

1H), 6.76 (d, J = 8.3 Hz, 1H), 7.13-7.16 (m, 1H), 7.29 (d, J = 2.7 Hz, 1H), 7.43 (s, 1H), 7.49-7.52 (m, 1H), 7.54 (s, 1H), 8.00 (s, 1H), 8.14 (s, 1H), 8.52 (d, J = 5.1 Hz, 1H), 8.55 (d, J = 9.0 Hz, 1H), 12.57 (brs, 1H)

Mass analysis, found (ESI-MS, m/z): 465, 467 ($M^+ + 1$)

[0100]

Example 21: N-{2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(6-methyl-2-pyridyl)urea

2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 6-amino-2-picoline (120 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 73 mg (yield 42%) of the titile compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.57 (s, 3H), 4.06 (s, 6H), 6.54 (d, J = 5.4 Hz, 1H), 6.66 (d, J = 8.1 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 7.15-7.18 (m, 1H), 7.30 (d, J = 2.7 Hz, 1H), 7.44 (s, 1H), 7.54-7.59 (m, 2H), 8.36 (s, 1H), 8.52 (d, J = 5.1 Hz, 1H), 8.57 (d, J = 9.0 Hz, 1H), 12.45 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 456, 467 ($M^+ + 1$)

[0101]

Example 22: N-{2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(4-methoxyphenyl)urea hydrochloride

2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]aniline (100 mg) was dissolved in chloroform (4 ml), and 4-methoxyphenyl isocyanate (60 µl) was then added to the solution. A reaction was then allowed to proceed at room temperature overnight. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added thereto. The resultant precipitate was collected by suction filtration to give 90 mg (yield 67%) of

N-2-chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl-N'-(4-methoxy-phenyl)urea. This product was suspended in 4 ml of methanol, and a hydrochloric acid-methanol solution was added to the suspension. The mixture was stirred at room temperature for 4 hr, and the solvent was then removed by distillation to give the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.73 (s, 3H), 4.03 (s, 3H), 4.05 (s, 3H), 6.90 (d, J = 9.3 Hz, 2H), 6.97 (d, J = 6.6 Hz, 1H), 7.37-7.41 (m, 3H), 7.62 (s, 1H), 7.67 (d, J = 2.7 Hz, 1H), 8.39 (d, J = 9.0 Hz, 1H), 8.49 (s, 1H), 8.82 (d, J = 6.6 Hz, 1H), 9.49 (s, 1H)

[0102]

Example 23: N-{2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(1-naphthyl)urea

2-Chloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]aniline (122 mg) was dissolved in chloroform (10 ml), and 1-naphthyl isocyanate (75 mg) was added to the solution. The mixture was stirred at room temperature overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution to precipitate a crystal. The crystal was collected by filtration to give 105 mg (yield 57%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.03 (s, 3H), 4.04 (s, 3H), 6.44 (d, J = 5.4 Hz, 1H), 6.72 (s, 1H), 7.10-7.13 (m, 3H), 7.41 (s, 1H), 7.48 (s, 1H), 7.55-7.69 (m, 4H), 7.88-7.96 (m, 2H), 8.15 (d, J = 7.6 Hz, 1H), 8.38-8.40 (m, 1H), 8.48 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 500, 502 (M^+ + 1)

[0103]

Example 24: N-(2, 4-Difluorophenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylaniline (710 mg) was dissolved in chloroform (7 ml), and 2, 4-difluorophenyl isocyanate (310 µl) was then added to the solution. The mixture was heated under reflux for one hr, and a large amount of ether was added to the reaction solution. The resultant precipitate was collected by suction filtration to give 735 mg (yield 70%) of the title compound.

[0104]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.14 (s, 3H), 2.27 (s, 3H), 4.04 (s, 3H), 4.06 (s, 3H), 6.27 (d, J = 5.4 Hz, 1H), 6.78-6.89 (m, 2H), 6.95 (s, 1H), 7.03 (d, J = 8.5 Hz, 1H), 7.10 (s, 1H), 7.40-7.45 (m, 2H), 7.61 (s, 1H), 8.03-8.12 (m, 1H), 8.46 (d, J = 5.4 Hz, 1H)

Mass analysis, found (FAB-MS, m/z): 480 (M^+ + 1)

[0105]

Example 25: N-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(3-fluoro-2-methoxyphenyl)urea

4-[(6, 7-Dimethoxy-4-quinoyl)oxy]-2, 3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 4-fluoro-2-methylaniline (126 µl) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (91/9) to give 160 mg (yield 91%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.12 (s, 3H), 2.22 (s, 3H), 2.25 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.24 (d, J = 5.1 Hz, 1H), 6.33 (s, 1H), 6.42 (s, 1H), 6.94-7.03 (m, 3H), 7.43 (s, 1H), 7.46-7.55 (m, 2H), 7.60 (s, 1H), 8.43 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 476 (M^+ + 1)

[0106]

Example 26: N-{4-[(6, 7-dimethoxy-4-quinoly)oxy]-2, 3-dimethylphenyl}-N'-(3-fluoro- 2-methoxyphenyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 3-fluoro-o-anisidine (132 µl) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol

was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (91/9) to give 23 mg (yield 13%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.15 (s, 3H), 2.32 (s, 3H), 3.84 (d, J = 1.7 Hz, 3H), 4.05 (s, 3H), 4.08 (s, 3H), 6.28 (d, J = 5.4 Hz, 1H), 6.72-6.77 (m, 1H), 6.96-7.09 (m, 3H), 7.43 (d, J = 8.5 Hz, 1H), 7.46 (s, 1H), 7.60 (s, 1H), 7.62 (s, 1H), 8.02-8.05 (m, 1H), 8.46 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 492 ($M^+ + 1$)

[0107]

Example 27: N-(5-Bromo-6-mehyl-2-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)-oxy]-2, 3-dimethylphenyl}urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethoylaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 6-amino-3-bromo-2-methylpyridine (208 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (91/9) to give 103 mg (yield 52%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.42 (s, 3H), 2.65 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.32 (d, J = 5.1 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.64 (s, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 8.29 (s, 1H), 8.45 (d, J = 5.4 Hz, 1H), 11.30 (brs, 1H)

Mass analysis, found (ESI-MS, m/z): 537, 539 ($M^+ + 1$)

[0108]

Example 28: N-(5-Chloro-2-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}urea

4-[(6,7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylaniline (3.00 g) was

dissolved in chloroform (150 ml) and triethylamine (6 ml), and a solution of triphosgene (2.74 g) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-amino-5-chloropyridine (2.38 g) was added to the reaction solution, and the mixture was then stirred at room temperature for additional 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by chromatography on silica gel by development with chloroform/methanol (20/1) to give 3.4 g (yield 77%) of the title compound.

[0109]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.38 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.31 (d, J = 5.4 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.62-7.68 (m, 2H), 7.90 (d, J = 8.8 Hz, 1H), 8.23 (d, J = 2.4 Hz, 1H), 8.45 (d, J = 5.4 Hz, 1H), 8.50 (s, 1H), 11.22 (brs, 1H)

Mass analysis, found (ESI-MS, m/z): 479, 481 ($M^+ + 1$)

[0110]

Example 29: N-(5-Bromo-2-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-amino-5-bromopyridine (192 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (91/9). The solvent was removed by distillation, and a crystal was precipitated from a minor amount of methanol and a large amount of ether. The crystal was collected by filtration to give 80 mg (yield 41%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.38 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.31 (d, J = 5.1 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 8.7 Hz, 1H), 7.45 (s, 1H), 7.64 (s, 1H), 7.75-7.77 (m, 1H), 7.89 (d, J = 8.8 Hz, 1H), 8.31 (d, J = 2.4 Hz, 1H), 8.45 (d, J = 5.4 Hz, 1H), 8.81 (s, 1H), 11.17 (brs, 1H)

Mass analysis, found (ESI-MS, m/z): 523, 525 ($M^+ + 1$)

[0111]

Example 30: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-2-methoxyphenyl)urea

4-[(6, 7-Dimetoxy-4-quinolyl)oxy]-2, 3-dimethyl-aniline (120 mg) was dissolved in chloroform (10 ml), and 2-methoxyphenyl isocyanate (60 µl) was added to the solution. The mixture was stirred at room temperature overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added thereto to precipitate a crystal which was then collected by filtration to give 131 mg (yield 75%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.32 (s, 3H), 3.81 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.25 (s, 1H), 6.26 (d, J = 5.4 Hz, 1H), 6.85-6.87 (m, 1H), 6.97-7.07 (m, 4H), 7.41 (d, J = 8.5 Hz, 1H), 7.44 (s, 1H), 7.62 (s, 1H), 8.15 – 8.17 (m, 1H), 8.45 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 474 ($M^+ + 1$)

[0112]

Example 31: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(2-methylphenyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml), and o-toluyl isocyanate (55 µm) was added to the solution. The mixture was stirred at room temperature overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution to precipitate a crystal which was then collected by filtration to give 130 mg (yield 70%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.12 (s, 3H), 2.22 (s, 3H), 2.26 (s, 3H), 4.05 (s, 3H), 4.07 (s, 3H), 6.23-6.28 (m, 3H), 7.02 (d, J = 8.5 MHz, 1H), 7.14-7.17 (m, 1H), 7.24-7.29 (m, 2H), 7.43 (s, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.60 (s, 1H), 7.63 (d, J = 7.3 Hz, 1H), 8.43 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 458 (M^+ + 1)

[0113]

Example 32: N-(4-Chloro-2-methylphenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 4-chloro-2-methylaniline (130 µl) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (91/9) to give 136 mg (yield 75%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.14 (s, 3H), 2.18 (s, 3H), 2.27 (s, 3H), 4.05 (s, 3H), 4.07 (s, 3H), 6.24 (d, J = 5.4 MHz, 1H), 6.33 (s, 1H), 6.40 (s, 1H), 7.03 (d, J = 8.5 Hz, 1H), 7.19-7.21 (m, 2H), 7.42-7.44 (m, 2H), 7.60 (s, 1H), 7.65 (d, J = 9.0 Hz, 1H), 8.44 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 492, 494 (M^+ + 1)

[0114]

Example 33: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(2-pyridyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethyaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-aminopyridine (104 mg) was added to the reaction solution, and the mixture was heated under reflux overnight. Methanol was

added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (91/9) to give 72 mg (yield 44%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.41 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.32 (d, J = 5.4 Hz, 1H), 6.92-6.98 (m, 2H), 7.04 (d, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.65 (s, 1H), 7.67-7.69 (m, 1H), 7.97 (d, J = 8.8 Hz, 1H), 8.25-8.27 (m, 1H), 8.45 (d, J = 5.1 Hz, 1H), 8.72 (s, 1H), 11.77 (br. 1H)

Mass analysis, found (ESI-MS, m/z): 445 (M^+ + 1)

[0115]

Example 34: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(5-methyl-2-pyridyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylaniline (120 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 2-amino-5-picoline (120 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 2 hr. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (91/9) to give 122 mg (yield 72%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.15 (s, 3H), 2.28 (s, 3H), 2.39 (s, 3H), 4.04 (s, 3H), 4.07 (s, 3H), 6.32 (d, J = 5.4 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 7.43 (s, 1H), 7.45-7.48 (m, 1H), 7.64 (s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 1.5 Hz, 1H), 8.44 (d, J = 5.4 Hz, 1H), 9.23 (s, 1H), 11.77 (br, 1H)

Mass analysis, found (FD-MS, m/z): 458 (M^+)

[0116]

Example 35: N-{4-[(6, 7-Dimethosy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(6-methyl-2-pyridyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylaniline (120 mg) was

dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (110 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 6-amino-2-picoline (120 mg) was added to the reaction solution, and the mixture was heated under reflux overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (40/60) to give 64 mg (yield 38%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.44 (s, 3H), 2.54 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.32 (d, J = 5.4 Hz, 1H), 6.61 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.53-7.57 (m, 1H), 7.65 (s, 1H), 7.79 (s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 8.44 (d, J = 5.1 Hz, 1H), 11.76 (br, 1H)

Mass analysis, found (FD-MS, m/z): 458 (M^+)

[0117]

Example 36: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylphenyl}-N'-(4-methoxyphenyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 3-dimethylaniline (100 mg) was dissolved in chloroform (4 ml) and 4-methoxyphenyl isocyanate (60 µl) was then added to the solution. The mixture was allowed to react at room temperature overnight, and the solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution. The resultant preciptate was then collected by suction filtration to give 115 mg (yield 78%) of the title compound.

[0118]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.02 (s, 3H), 2.30 (s, 3H), 3.76 (s, 3H), 4.06 (s, 3H), 4.12 (s, 3H), 6.46 (d, J = 6.3 Hz, 1H), 6.78 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 9.0 Hz, 2H), 7.67 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.92 (s, 1H), 8.20-8.23 (m, 1H)

Mass analysis, found (ESI-MS, m/z): 474 ($M^+ + 1$)

[0119]

Example 37: N-(2, 4-Difluorophenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylaniline (200 mg) was dissolved in chloroform (15 ml) and 2, 4-difluorophenyl isocyanate (88 μl) was then added to the solution. The mixture was heated under reflux for one hr. The reaction solution was purified by chromatography on silica gel by development with chloroform/acetone (4/1) to give 287 mg (yield 97%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.26 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.31 (d, J = 5.4 Hz, 1H), 6.57 (s, 1H), 6.81-6.95 (m, 3H), 7.00 (s, 1H), 7.43 (s, 1H), 7.55 (s, 1H), 7.59 (s, 1H), 8.05-8.13 (m, 1H), 8.47 (d, J = 5.4 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 479 (M^+)

[0120]

Example 38: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-propylurea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylaniline (150 mg) was dissolved in chloroform (13 ml) and triethylamine (1.5 ml), and a solution of triphosgene (151 mg) in chloroform was then added to the solution. The mixture was heated under reflux for 5 min. Next, n-prpylamine (33 mg) was added to the reaction solution, and the mixture was heated under reflux for additional 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was supported on diatomaceous earth, followed by extraction with chloroform. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (4/1) to give 178 mg (yield 95%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.94 (t, J = 7.3 Hz, 3H), 1.51-1.65 (m, 2H), 2.15 (s, 3H), 2.26 (s, 3H), 3.21-3.28 (m, 2H), 4.05 (s, 3H), 4.06 (s, 3H), 4.63-4.69 (m, 1H), 5.97 (s, 1H), 6.31 (d, J = 5.1 Hz, 1H), 6,98 (s, 1H), 7.43 (s, 2H), 7.58 (s, 1H), 8.46 (d, J = 5.4 Hz, 1H)

Mass analysis, found (FD-MS, m/z): 409 (M^+)

[0121]

Example 39: N-(4-Chloro-2-methylphenyl)-N'-{4[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylaniline (100 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (92 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 4-chloro-2-methylaniline (44 µl) was added to the reaction solution, and the mixture was stirred at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution to precipitate a crystal which was then collected by filtration to give 118 mg (yield 78%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.21 (s, 3H), 2.23 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.28 (d, J = 5.4 Hz, 1H), 6.30 (s, 1H), 6.32 (s, 1H), 6,98 (s, 1H), 7.22-7.23 (m, 2H), 7.43 (s, 1H), 7.58 (s, 1H), 7.59-7.63 (m, 2H), 8.45 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 492, 494 (M^+ + 1)

[0122]

Example 40: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(4-fluoro-2-methylphenyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylaniline (100 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (92 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 4-chloro-2-methylaniline (42 µl) was added to the reaction solution, and the mixture was stirred at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large

amount of ether was added to the solution to precipitate a crystal which was then collected by filtration to give 108 mg (yield 74%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.15 (s, 6H), 2.30 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.24 (s, 2H), 6.28 (d, J = 5.1 Hz, 1H), 6.94 (s, 1H), 6.96-7.00 (m, 2H), 7.42 (s, 1H), 7.49-7.52 (m, 1H), 7.58 (s, 1H), 7.64 (s, 1H), 8.44 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 476 (M^+ + 1)

[0123]

Example 41: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(3-fluoro-2-methoxyphenyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylaniline (100 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (92 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 3-fluoro-o-anisidine (44 µl) was added to the reaction solution, and the mixture was stirred at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 126 mg (yield 83%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H), 2.27 (s, 3H), 3.83 (d, J = 1.7 Hz, 3H), 4.04 (s, 3H), 4.07 (s, 3H), 6.31 (d, J = 5.1 Hz, 1H), 6.74-6.79 (m, 1H), 6.97-7.03 (m, 3H), 7.44 (s, 1H), 7.57 (s, 1H), 7.60 (s, 1H), 7.66 (s, 1H), 8.02-8.04 (m, 1H), 8.48 (d, J = 5.1 Hz, 1H)

Mass analysis, fond (ESI-MS, m/z): 492 (M^+ + 1)

[0124]

Example 42: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(2-methylphenyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylaniline (100 mg) was dissolved in chloroform (10 ml), and o-toluyl isocyanate (46 µl) was added to the solution. The mixture was stirred at room temperature overnight. Methanol was

added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 111 mg (yield 79%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.12 (s, 6H), 2.26 (s, 3H), 4.03 (s, 3H), 4.05 (s, 3H), 6.27 (d, J = 5.1 Hz, 1H), 6.77 (s, 1H), 6.81 (s, 1H), 6.91 (s, 1H), 7.11-7.15 (m, 1H), 7.22 (s, 1H), 7.24 (s, 1H), 7.42 (s, 1H), 7.59 (s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.68 (s, 1H), 8.43 (d, J = 5.4 Hz, 1H)

Mass analysis, found (ESI-MS, m/z); 458 (M^+ + 1)

[0125]

Example 43: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(2-methoxyphenyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylaniline (100 mg) was dissolved in chloroform (10 ml), and 2-methoxyphenyl isocyanate (49 µl) was added to the solution. The mixture was stirred at room temperature overnight. Methanol was added to the reaction solution, and the solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to quantitatively give the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.14 (s, 3H), 2.24 (s, 3H), 3.75 (s, 3H), 4.03 (s, 3H), 4.07 (s, 3H), 6.31 (d, J = 5.1 Hz, 1H), 6.84-6.87 (m, 1H), 6.95-7.03 (m, 3H), 7.06 (s, 1H), 7.44 (s, 1H), 7.56 (s, 1H), 7.61 (s, 1H), 7.63 (s, 1H), 8.17-8.20 (m, 1H), 8.46 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 474 (M^+ + 1)

[0126]

Example 44: N-(5-Bromo-6-methyl-2-pyridyl)-N'-{4-[(6,7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylaniline (100 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (92 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 6-amino-3-bromo-2-methylpyridine (69 mg) was

added to the reaction solution, and the mixture was stirred at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution to precipitate a crystal which was then collected by filtration to give 80 mg (yield 48%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.18 (s, 3H), 2.42 (s, 3H), 2.65 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.34 (d, J = 5.4 Hz, 1H), 6.57 (d, J = 8.5 Hz, 1H), 6,98 (s, 1H), 7.43 (s, 1H), 7.62 (s, 1H), 7.70 (s, 1H), 7.74 (d, J = 8.5 Hz, 1H), 8.05 (s, 1H), 8.46 (d, J = 5.4 Hz, 1H), 11.17 (br, 1H)

Mass analysis, found (ESI-MS, m/z): 537, 539 ($M^+ + 1$)

[0127]

Example 45: N-(2, 6-Dimethoxy-3-pyridyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylaniline (100 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (92 mg) in dichloromethane was then added to the solution. The mixture was stirred at room temperature for 30 min. Next, 3-amino-2, 6-dimethoxypyridine (70 mg) was added to the reaction solution, and the mixture was stirred at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution to precipitate a crystal which was then collected by filtration to give 124 mg (yield 79%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.27 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 4.06 (s, 3H), 4.07 (s, 3H), 6.31 (d, J = 5.1 Hz, 1H), 6.34 (d, J = 8.5 Hz, 1H), 6.36 (s, 1H), 6.74 (s, 1H), 6.99 (s, 1H), 7.44 (s, 1H),7.57 (s, 1H), 7.60 (s, 1H), 8.20 (d, J = 8.3 Hz, 1H), 8.46 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 505 ($M^+ + 1$)

[0128]

Example 46: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylphenyl}-N'-(4-methoxyphenyl)urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2, 5-dimethylaniline (100 mg) was dissolved in chloroform (4 ml), and 4-methoxyphenyl isocyanate (60 μm) was then added to the solution. The mixture was allowed to react at room temperature overnight. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in a minor amount of chloroform, and a large amount of ether was added to the solution. The resultant precipitate was collected by suction filtration to give to 110 mg (yield 74%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.07 (s, 3H), 2.26 (s, 3H), 3.76 (s, 3H), 4.03 (s, 3H), 4.08 (s, 3H), 6.39 (d, J = 6.1 Hz, 1H), 6.80 (d, J = 9.0 Hz, 2H), 6.87 (s, 1H), 7.36 (d, J = 9.0 Hz, 2H), 7.55 (br, 1H), 7.62 (s, 1H), 7.67 (s, 1H), 7.80 (s, 1H), 8.19 (br, 1H), 8.27 (d, J = 6.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 474 ($M^+ + 1$)

[0129]

Example 47: N-{4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-nitrophenyl}-N'-propylurea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-nitroaniline (150 mg) was dissolved in chloroform (10 ml) and triethylamine (1.5 ml), and a solution of triphosgene (144 mg) in chloroform was then added to the solution. The mixture was heated under reflux for 5 min. Next, n-propylamine (31 mg) was added. The mixture was heated under reflux for additional 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was supported on diatomaceous earth, followed by extraction with chloroform. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (4/1) to give 160 mg (yield 86%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.01 (t, J = 7.5 Hz, 3H), 1.59-1.69 (m, 2H), 3.27-3.34 (m, 2H), 4.05 (s, 3H), 4.06 (s, 3H), 4.95-5.01 (br, 1H), 6.47 (d, J = 5.4 Hz,

1H), 7.43-7.51 (m, 3H), 8.04 (d, J = 2.7 Hz, 1H), 8.53 (d, J = 5.4 Hz, 1H), 8.81 (d, J = 9.3 Hz, 1H), 9.74-9.79 (br, 1H)

Mass analysis, found (FD-MS, m/z): 426 (M^+)

[0130]

Example 48: N-(2, 4-Difluorophenyl)-N'-{4-[(6, 7-dimethoxy-4-quinolyl)oxy]-2-nitrophenyl}urea

4-[(6, 7-Dimethoxy-4-quinolyl)oxy]-2-nitroaniline (100 mg) was dissolved in chloroform (10 ml) and triethylamine (1 ml), and a solution of triphosgene (96 mg) in chloroform was then added to the solution. The mixture was heated under reflux for 5 min. Next, 2, 4-difluoroaniline (45 mg) was added to the reaction solution, and the mixture was further heated under reflux overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was supported on diatomaceous earth, followed by extraction with chloroform. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/acetone (3/1) to give 81 mg (yield 56%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 4.06 (s, 3H), 6.50 (d, J = 5.1 Hz, 1H), 6.91-6.98 (m, 3H), 7.45 (s, 1H), 7.49 (s, 1H), 7.50-7.54 (m, 1H), 7.88-7.97 (m, 1H),8.05 (d, J = 2.9 Hz, 1H), 8.54 (d, J = 5.1 Hz, 1H), 8.77 (d, J = 9.3 Hz, 1H), 9.98 (s, 1H)

Mass analysis, found (FD-MS, m/z): 496 (M^+)

[0131]

Example 49: N-{3, 5-Dichloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]phenyl}-N'-(2, 4-difluorophenyl)urea

3.5-Dichloro-4-[(6, 7-dimethoxy-4-quinolyl)oxy]aniline (53 mg) was dissolved in chloroform (5 ml), and 2, 4-difluorophenyl isocyanate (34 μl) was added to the solution. The mixture was heated under reflux overnight. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 56 mg (yield 74%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 3H), 4.09 (s, 3H), 6.26 (d, J = 5.4 Hz,

1H), 6.86-6.93 (m, 2H), 7.05 (s, 1H), 7.44 (s, 1H), 7.46 (s, 1H), 7.60 (s, 2H), 7.64 (s, 1H),8.01-8.05 (m, 1H), 8.48 (d, J = 5.4 Hz, 1H)

Mass analysis, found (FAB-MS, m/z): 520, 522, 524 ($M^+ + 1$)

[0132]

Example 50: N-(2, 4-Difluorophenyl)-N'-(2-fluoro-4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}phenyl)urea

N-(2, 4-Difluorophenyl)-N'-{2-fluoro-4-[(7-hydroxy-6-methoxy-4-quinolyl)oxy]-phenyl}urea (20 mg), potassium carbonate (7 mg), tetra-n-butylammonium iodide (20 mg), N-(2-chloroethyl)morpholino hydrochloride (10 mg) were dissolved in N, N-dimethylformamide (1 ml), and the solution was stirred at 70℃ overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (30/1) to give 14 mg (yield 57%) of the title compound.

[0133]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.57 (t. J = 4.4 Hz, 4H), 2.88 (m, 2H), 3.69 (t, J = 4.4 Hz, 4H), 3.94 (s, 3H), 4.26 (t, J = 5.9 Hz, 2H), 6.43 (d, J = 5.1 Hz, 1H), 6.77-6.95 (m, 4H), 7.35 (s, 1H), 7.43 (s, 1H), 7.96-8.02 (m, 1H), 8.13-8.17 (m, 1H), 8.44 (d, J = 5.1 Hz, 1H)

[0134]

Example 51: N-(2-Chloro-4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}-phenyl)-N'-(2,4-difluorophenyl)urea

N-{2-Chloro-4-[(7-hydroxy-6-methoxy-4-quinolyl)-oxy]phenyl}-N'-(2, 4-difluorophenyl) urea (174 mg) was dissolved in N, N-dimethylformamide (9 ml), and potassium carbonate (64 mg), tetra-n-butylammonium iodide (14 mg), and N-(2-chloroethyl)- morpholine hydrochloride (86 mg) were then added to the solution. The mixture was stirred at 70℃ for 17 hr, and a saturated aqueous sodium

hydrogencarbonate solution was then added to the reaction solution, followed by extraction with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (20/1) to give 75 mg (yield 35%) of the title compound.

[0135]

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.60-2.67 (m, 4H), 2.95 (t, J = 6.0 Hz, 2H), 3.71-3.79 (m, 4H), 4.01 (s, 3H), 4.33 (t, J = 6.0 Hz, 2H), 6.50 (d, J = 5.1 Hz, 1H), 6.85-6.97 (m, 2H), 7.09-7.17 (m, 2H), 7.22-7.27 (m, 2H), 7.42 (s, 1H), 7.50 (s, 1H), 7.97-8.01 (m, 1H), 8.28 (d, J = 9.0 Hz, 1H), 8.51 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 585, 587 ($M^+ + 1$)

[0136]

Example 52: N-(2, 4-Difluorophenyl)-N'-(4-{[6-methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}-2, 5-dimethylphenyl)urea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]-oxy}-2, 5-dimethylphenyl)-N'-(2, 4-difluorophenyl)urea (366 mg) was dissolved in N, N-dimethylformamide (6 ml), and palladium hydroxide (366 mg) was added to the solution. The mixture was stirred in a hydrogen atmosphere at room temperature overnight. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in chloroform and methanol. The reaction solution was filtered through Celite. Next, the solvent was removed by distillation under the reduced pressure. The residue (213 mg), potassium carbonate (109 mg), tetra-n-butylammonium iodide (12 mg), and N-(2-chloroethyl)morphline hydrochloride (74 mg) were dissolved in N, N-dimethylformamide (5 ml), and the solution was stirred at 70℃ overnight. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (10/1) to give 106 mg (yield 55%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.27 (s, 3H), 2.64 (t, J = 4.6 Hz, 4H) 2,96 (t, J = 6.0 Hz, 2H), 3.76 (t, J = 4.6 Hz, 4H), 4.03 (s, 3H), 4.34 (t, J = 6.0 Hz, 2H), 6.31 (d, J = 5.4 Hz, 1H), 6.47 (2, 1H), 6.81-6.92 (m, 3H), 7.00 (s, 1H), 7.43 (s, 1H), 7.54 (s, 1H), 7.58 (s, 1H), 8.05-8.12 (m, 1H), 8.47 (d, J = 5.4 Hz, 1H)

[0137]

Example 53: N-(4-{[6-Methoxy-7-(2-morpholinoethoxy)-4-quinolyl]oxy}-2, 5-dimethylphenyl)-N'-(2-methoxyphenyl)urea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]-oxy}-2, 5-dimethylphenyl)-N'-(2-methoxyphenyl)urea (363 mg) was dissolved in N, N-dimethylformamide (6 ml), and palladium hydroxide (366 mg) was added to the solution. The mixture was stirred in a hydrogen atmosphere at room temperature overnight. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in chloroform and methanol, and the solution was filtered through Celite. Next, the solvent was removed by distillation under the reduced pressure. The residue (191 mg), potassium carbonate (219 mg), tetra-n-butylammonium iodide (12 mg), and N-(2-chloroethyl)-morphline hydrochloride (148 mg) were dissolved in N, N-dimethylformamide (5 ml). The solution was stirred at 70℃ overnight. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (10/1) to give 101 mg (yield 55%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2,28 (s, 3H), 2.64 (t, J = 4.5 Hz, 4H), 2.96 (t, J = 5.9 Hz, 2H), 3.76 (t, J = 4.6 Hz, 4H), 3.83 (s, 3H), 4.04 (s, 3H), 4.34 (t, J = 6.0 Hz, 2H), 6.30 (d, J = 5.4 Hz, 2H), 6.86-6.90 (m, 1H), 6.96-7.06 (m, 3H), 7.16 (s, 1H), 7.43 (s, 1H), 7.57 (s, 1H), 7.59 (s, 1H), 8.11-8.16 (m, 1H), 8.46 (d, J = 5.4 Hz, 1H)

[0138]

Example 54: N-(2-Chloro-4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}-N'-(2, 4-difluorophenyl)urea

Sodium hydride (60 wt%, 153 mg) was added to dimethyl sulfoxide (2 ml), and

the mixture was stirred at 60℃ for 30 min and was then cooled to room temperature. 4-Amino-3-chlorophenol hydrochloride (343 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 10 min. Next, a solution of 4-chloro-6-methoxy-7-(2-methoxyethoxy)-quinoline (254 mg) in dimethyl sulfoxide (2 ml) was added to the reaction solution. The mixture was stirred at 110℃ overnight. Water was added to the reaction solution, followed by extraction with chloroform. The chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (7/3) to give 332 mg of a mixture containing 2-chloro-4-{[(6-methoxy-7-(2-methoxyethoxy)-4- quinolyl]oxy}aniline as a major product. A 83 mg portion of the mixture was dissolved in chloroform (5 ml), and 2, 4-difluorophenyl isocyanate (32 μl) was added to the solution. The mixture was heated under reflux overnight. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 50 mg of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.75-3.77 (m, 2H), 3.94 (s, 3H), 4.27-4.29 (m, 2H), 6.55 (d, J = 5.1 Hz, 1H), 7.04-7.09 (m, 1H), 7.25-7.36 (m, 2H), 7.42 (s, 1H), 7.50 (s, 1H), 7.51 (s, 1H), 8.09-8.15 (m, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.49 (d, J = 5.4 Hz, 1H), 8.82 (s, 1H), 9.31 (s, 1H)

[0139]

Example 55: N-(2-Chloro-4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}phenyl)-N'-(2-methoxyphenyl)urea

Sodium hydride (60 wt%, 153 mg) was added to dimethyl sulfoxide (2 ml), and the mixture was stirred at 60℃ for 30 min and was then cooled to room temperature. 4-Amino-3-chllorophnol hydrochloride (343 mg) was added to the reaction solution, and the mixture was stirred at room temperature for 10 min. Next, a solution of 4-chloro-6-methoxy-7-(2-methoxyethoxy)quinoline (254 mg) in dimethyl sulfoxide (2 ml) was added to the reaction solution, and the mixture was stirred at 110℃ overnight. Water was added to the reaction solution, followed by extraction with chloroform. The

chloroform layer was then washed with a saturated aqueous sodium hydrogencarbonate solution and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (7/3) to give 332 mg of a mixture containing 2-chloro-4-{[(6-methoxy-7-(2-methoxyethoxy)-4-quinolyl)oxy}aniline as a main product. A 83 mg portion of the mixture was dissolved in chloroform (5 ml), and 2-methoxyphenyl isocyanate (35 μl) was added to the solution. The mixture was heated under reflux overnight. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/acetone (2/1) to give 31 mg of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.75 4.27-3.77 (m, 2H), 3.90 (s, 3H), 3.94 (s, 3H), 4.27-4.29 (m, 2H), 6.55 (d, J = 5.1 Hz, 1H), 6.89-7.05 (m, 3H), 7.24-7.27 (m, 1H), 7.42 (s, 1H), 7.48 (d, J = 2.7 Hz, 1H), 7.50 (s, 1H), 8.08-8.11 (m, 1H), 8.18-8.22 (m, 1H), 8.49 (d, J = 5.4 Hz, 1H), 8.99-9.03 (m, 2H)

[0140]

Example 56: N-(2, 4-Difluorophenyl)-N'-(4-{[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}-2, 3-dimethylphenyl)urea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2, 3-dimethylphenyl)-N'-(2, 4-difluorophenyl)urea (213 mg) was dissolved in N, N-dimethylformamide (5 ml) and triethylamine (1 ml), and palladium hydroxide (40 mg) was added to the solution. The mixture was stirred in a hydrogen atmosphere at room temperature overnight. The reaction solution was filtered through Celite and was then washed with chloroform/ methanol. The solvent was removed by distillation under the reduced pressure. A 90 mg portion of the residue (184 mg) was dissolved in N, N-dimethylformamide (1.5 ml), and potassium carbonate (32 mg), tetra-n-btylammonium iodide (7 mg), and 2-bromoethyl methyl ether (32 mg) were added to the solution. The mixture was stirred at 70℃ overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer

chromatography on silica gel by development with chloroform/acetone (2/1) to give 110 mg of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.97 (s, 3H), 2.17 (s, 3H), 3.31 (s, 3H), 3.70 (t, J = 4.4 Hz, 2H), 3.90 (s, 3H), 4.21 (t, J = 4.4 Hz, 2H), 6.18 (d, J = 5.1 Hz, 1H), 6.95-6.98 (m, 2H), 7.22-7.31 (m, 1H), 7.34 (s, 1H), 7.51 (s, 1H), 7.62 (d, J = 8.8 Hz, 1H), 8.03-8.10 (m, 1H), 8.36 (d, J = 5.1 Hz, 1H), 8.38 (s, 1H), 8.79 (s, 1H)

[0141]

Example 57: N-(4-{[6-Methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy}-2, 3-dimethylphenyl)-N'-(2-methoxyphenyl)urea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2, 3-dimethylphenyl)-N'-(2-methoxyphenyl) urea (161 mg) was dissolved in N, N-dimethylformamide (4 ml) and triethylamine (1 ml), and palladium hydroxside (32 mg) was added to the solution. The mixture was stirred in a hydrogen atmosphere at room temperature overnight. The reaction solution was filtered through Celite and was washed with chloroform/methanol. The solvent was removed by distillation under the reduced pressure. A 110 mg portion of the residue (223 mg) was dissolved in N, N-dimethylformamide (1.5 ml), and potassium carbonate (23 mg), tetra-n-butylammonium iodide (5 mg), and 2-bromoethyl methyl ether (23 mg) were added to the solution. The mixture was stirred at 70℃ overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/acetone (2/1) to give 89 mg of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.00 (s, 3H), 2.17 (s, 3H), 3.70 (t, J = 4.2 Hz, 2H), 3.83 (s, 3H), 3.90 (s, 3H), 4.22 (t, J = 4.2 Hz, 2H), 6.19 (d, J = 5.1 Hz, 1H), 6.81-6.88 (m, 2H), 6.94-6.97 (m, 2H), 7.34 (s, 1H), 7.51 (s, 1H), 7.58 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 8.36 (d, J = 5.1 Hz, 1H), 8.48 (s, 1H), 8.58 (s, 1H)

[0142]

Example 58: N-(2, 4-Dfluorophenyl)-N'-(4-{[6-methoxy-7-(2-methoxyethoxy-4-

quinolyl)oxy]-2, 5-dimethylphenyl}urea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2, 5-dimethylphenyl)-N'-(2, 4-difluorophenyl)urea (366 mg) was dissolved in N, N-dimethylformamide (6 ml), and palladium hydroxide (366 mg) was added to the solution. The mixture was stirred in a hydrogen atmosphere at room temperature overnight. The solvent was removed by distillation under the reduced pressure. The residue was dissolved in chloroform and methanol, and the solution was filtered through Celite. Next, the solvent was removed by distillation under the reduced pressure. The residue (213 mg), potassium carbonate (109 mg), tetra-n-butylammonium iodide (12 mg), and 2-bromoethyl methyl ether (40 μl) were dissolved in N, N-dimethylformamide (5 ml), and the solution was stirred at 70℃ overnight. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (10/1) to give 124 mg (yield 73%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.26 (s, 3H), 3.49 (s, 3H), 3.90 (t, J = 4.8 Hz, 2H), 4.03 (s, 3H), 4.34 (t, J = 4.8 Hz, 2H), 6.30 (d, J = 5.1 Hz, 1H), 6.57 (s, 1H), 6.81-6.95 (m, 3H), 7.00 (s, 1H), 7.43 (s, 1H), 7.55 (s, 1H), 7.57 (s, 1H), 8.05-8.14 (m, 1H), 8.46 (d, J = 5.4 Hz, 1H)

Mass layer, found (ESI-MS, m/z): 524 (M^+ + 1)

[0143]

Example 59: N-(4-{[6-Methoxy-7-(2-methoxyethoxy)-4-quinolyul]oxy}-2, 5-dimethylphenyl)-N'-(2-methoxyphenyl)urea

N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2, 5-dimethylphenyl)-N'-(2-methoxyphenyl)urea (363 mg) was dissolved in N, N-dimethylformamide (6 ml), and palladium hydroxide (363 mg) was added to the solution. The mixture was stirred in a hydrogen atmosphere at room temperature overnight. The solvent was removed by distillation under the reduced pressure, and the residue was dissolved in chloroform and methanol. The solution was filtered through Celite. Next, the solvent was removed

by distillation under the reduced pressure. The residue (191 mg), potassium carbonate (110 mg), tetra-n-butylammonium iodide (12 mg), and 2-bromoethyl methyl ether (80 mg) were dissolved in N, N-dimethylformamide (5 ml), and solution was stirred at 70℃ overnight. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/methanol (10/1) to give 128 mg (yield 76%) of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 3H), 2.28 (s, 3H), 3.49 (s, 3H), 3,83 (s, 3H), 3.90 (t, J = 4.8 Hz, 2H), 4.04 (s, 3H), 4.35 (t, J = 4.9 Hz, 2H), 6.30 (d, J = 5.4 Hz, 1H), 6.33 (s, 1H), 6.86-6.90 (m, 1H), 6.96-7.06 (m, 3H), 7.17 (s, 1H), 7.43 (s, 1H), 7.56 (s, 1H), 7.58 (s, 1H), 8.12-8.17 (m, 1H), 8.45 (d, J = 5.1 Hz, 1H)

Mass analysis, found (ESI-MS, m/z): 518 ($M^+ + 1$)

[0144]

Example 60: N-(4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2, 3-dimethylphenyl)-N'-(2-methoxyphenyl)urea

4-{[7-(Benzyloxy)-6-methoxy-4-quinolyl]oxy}-2, 3-dimethylaniline (260 mg) was dissolved in N, N-dimethylformamide (5 ml), and 2-methoxyphyenyl isocyanate (116 mg) was then added to the solution. The mixture was allowed to react at room temperature overnight. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by thin-layer chromatography on silica gel by development with chloroform/acetone (2/1) to give 169 mg (yield 47%) of the title compound.

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 1.99 (s, 3H), 2.02 (s, 3H), 3.83 (s, 3H), 3.90 (s, 3H), 5.25 (s, 2H), 6.18 (d, J = 5.3 Hz, 1H), 6.81-6.87 (m, 2H), 6.95 (d, J = 6.1 Hz, 1H), 7.29-7.59 (m, 7H), 8.07 (d, J = 6.1 Hz, 1H), 8.35 (d, J = 5.3 Hz, 1H), 8.48 (s, 1H), 8.58 (s, 1H)

[0145]

Example 61: N-{2-Chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}-N'-(2, 4-difluorophenyl)urea

2-Chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]-aniline (214 mg) was dissolved in chloroform (5 ml), and 2, 4-difluorophenyl isocyanate (180 μl) was then added to the solution. The mixture was allowed to react at 70℃ for 4 hr, and a large amount of ether was added to the reaction solution. The resultant precipitate was collected by suction filtration to give 146 mg (yield 46%) of the title compound.

[0146]

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 3.98 (s, 3H), 3.99 (s, 3H), 7.03-7.10 (m, 1H), 7.28-7.37 (m, 2H), 7.40 (s, 1H), 7.56 (s, 2H), 8.08-8.21 (m, 2H), 8.57 (s, 1H), 8.80 (s, 1H), 9.30 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 487, 489 ($M^+ + 1$)

[0147]

Example 62: N-{2-Chloro-4-[(6, 7-dimethoxy-4-quinazolinyl)oxy]phenyl}- N'-propylurea

2-Chloro-4-[(6, 7-dimethoxy-4-qunazolinyl)oxy]-aniline (5.13 g) was dissolved in chloroform (100 ml) and triethylamine (50 ml), and a solution of triphosgene (4.59 g) in chloroform (1 ml) was then added to the solution. The mixture was stirred for 30 min. Next, n-propylamine (2.74 g) was added to the reaction solution, and the mixture was stirred for additional 2 hr. A saturated aqueous sodium hydrogencarbonate solution was added to the reaction solution, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by chromatography on silica gel by development with chloroform/methanol (50/1) to give 4.14 g (yield 64%) of the title compound.

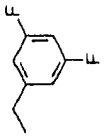
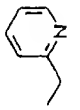
^{1}H-NMR (DMSO-d_6, 400 MHz): δ 0.91 (t, J = 7.3 Hz, 3H), 1.41-1.53 (m, 2H), 3.05-3.12 (m, 2H), 3.97 (s, 3H), 3.99 (s, 3H), 6. 99 (t, J = 5.4 Hz, 1H), 7.22 (dd, J = 2.7 Hz, 9.0 Hz, 1H), 7.38 (s, 1H), 7.46 (d, J = 2.9 Hz, 1H), 7.54 (s, 1H), 8.04 (s, 1H), 8.20 (d, J = 9.3 Hz, 1H), 8.55 (s, 1H)

Mass analysis, found (ESI-MS, m/z): 417 ($M^+ + 1$)

The structures of the compounds described in the examples are as follows.

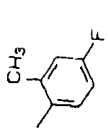
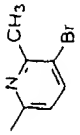
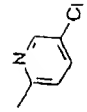
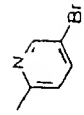
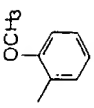
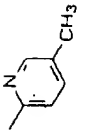
[0148]

[Table 1]

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
1	CH	CH	H	CH_3O	CH_3O	H	H	H	H	F	H	H	
2	CH	CH	H	CH_3O	CH_3O	H	H	H	H	F	H	H	
3	CH	CH	H	CH_3O	CH_3O	H	H	H	H	F	H	H	
4	CH	CH	H	CH_3O	CH_3O	H	H	H	H	F	H	H	
5	CH	CH	H	CH_3O	CH_3O	H	H	H	H	F	H	H	
6	CH	CH	H	CH_3O	CH_3O	H	H	H	H	F	H	H	
7	CH	CH	H	CH_3O	CH_3O	H	H	H	H	F	H	H	
8	CH	CH	H	CH_3O	CH_3O	H	H	H	H	F	H	H	
9	CH	CH	H	CH_3O	CH_3O	H	H	H	H	F	H	H	
10	CH	CH	H	CH_3O	CH_3O	H	H	H	H	F	H	H	

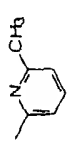
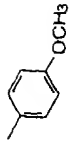
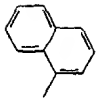
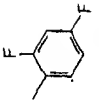
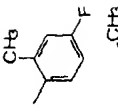
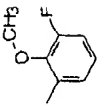
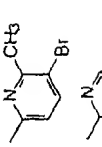
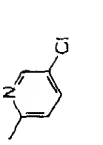
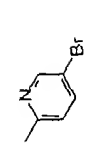
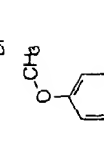
[0149]

[Table 2]

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
11	CH	CH	H	CH_3O	CH_3O	H	H	H	H	F	H	H	
12	CH	CH	H	CH_3O	CH_3O	H	H	H	H	F	H	H	
13	CH	CH	H	CH_3O	CH_3O	H	H	H	H	Cl	H	H	
14	CH	CH	H	CH_3O	CH_3O	H	H	H	H	Cl	H	H	
15	CH	CH	H	CH_3O	CH_3O	H	H	H	H	Cl	H	H	
16	CH	CH	H	CH_3O	CH_3O	H	H	H	H	Cl	H	H	
17	CH	CH	H	CH_3O	CH_3O	H	H	H	H	Cl	H	H	
18	CH	CH	H	CH_3O	CH_3O	H	H	H	H	Cl	H	H	
19	CH	CH	H	CH_3O	CH_3O	H	H	H	H	Cl	H	H	
20	CH	CH	H	CH_3O	CH_3O	H	H	H	H	Cl	H	H	

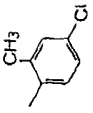
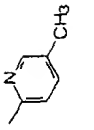
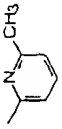
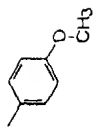
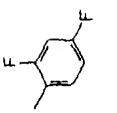
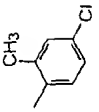
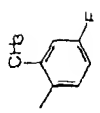
[0150]

[Table 3]

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
21	CH	CH	H	CH_3O	CH_3O	H	H	H	H	Cl	H	H	
22	CH	CH	H	CH_3O	CH_3O	H	H	H	H	Cl	H	H	
23	CH	CH	H	CH_3O	CH_3O	H	H	H	H	Cl	H	H	
24	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
25	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
26	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
27	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
28	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
29	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
30	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	

[0151]

[Table 4]

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
31	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
32	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
33	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
34	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
35	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
36	CH	CH	H	CH_3O	CH_3O	H	CH_3	CH_3	H	H	H	H	
37	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
38	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
39	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
40	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	

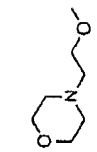
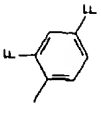
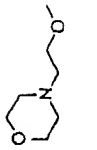
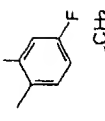
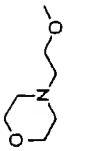
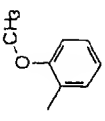
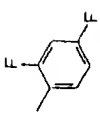
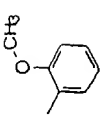
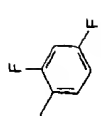
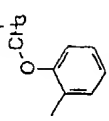
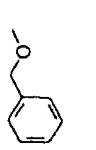
[0152]

[Table 5]

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
41	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
42	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
43	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
44	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
45	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
46	CH	CH	H	CH_3O	CH_3O	H	H	CH_3	CH_3	H	H	H	
47	CH	CH	H	CH_3O	CH_3O	H	H	NO_2	H	H	H	H	
48	CH	CH	H	CH_3O	CH_3O	H	H	NO_2	H	H	H	H	
49	CH	CH	H	CH_3O	CH_3O	H	Cl	H	Cl	H	H	H	
50	CH	CH	H	CH_3O		H	H	H	H	F	H	H	

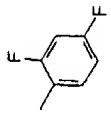
[0153]

[Table 6]

	X	Z	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
51	CH	CH	H	CH_3O		H	H	H	H	Cl	H	H	
52	CH	CH	H	CH_3O		H	H	CH_3	CH_3	H	H	H	
53	CH	CH	H	CH_3O		H	H	CH_3	CH_3	H	H	H	
54	CH	CH	H	CH_3O	$CH_3O(CH_2)_2O$	H	H	H	H	Cl	H	H	
55	CH	CH	H	CH_3O	$CH_3O(CH_2)_2O$	H	H	H	H	Cl	H	H	
56	CH	CH	H	CH_3O	$CH_3O(CH_2)_2O$	H	CH_3	CH_3	H	H	H	H	
57	CH	CH	H	CH_3O	$CH_3O(CH_2)_2O$	H	CH_3	CH_3	H	H	H	H	
58	CH	CH	H	CH_3O	$CH_3O(CH_2)_2O$	H	H	CH_3	CH_3	H	H	H	
59	CH	CH	H	CH_3O	$CH_3O(CH_2)_2O$	H	H	CH_3	CH_3	H	H	H	
60	CH	CH	H	CH_3O		H	CH_3	CH_3	H	H	H	H	

[0154]

[Table 7]

	X	Z	R^1	R^2	R^3	R^5	R^6	R^7	R^8	R^9	R^{10}	R^{11}
61	N	CH	H	CH_3O	CH_3O	H	H	H	Cl	H	H	
62	N	CH	H	CH_3O	CH_3O	H	H	H	Cl	H	H	
63	N	CH	H	CH_3O	CH_3O	H	Cl	H	H	H	H	
64	N	CH	H	CH_3O	CH_3O	H	Cl	H	H	H	H	
65	N	CH	H	CH_3O	CH_3O	H	Cl	H	H	H	H	
66	N	CH	H	CH_3O	CH_3O	H	Cl	H	H	H	H	
67	N	CH	H	CH_3O	CH_3O	H	Cl	H	H	H	H	
68	N	CH	H	CH_3O	CH_3O	H	Cl	H	H	H	H	

[0155]

Pharmacological Test Example 1: Measurement of inhibitory activity against activation of MAPK within vascular endothelial cells induced by VEGF stimulation

Human funicular venous vasculae endothlial cells (purchased from Chronetics) were cultured in an EGM-2 medium (purchased from Chronetics) within an incubator containing 5% carbon dioxide until 50 to 70% confluent, and the culture was inoculated into wells, containing the same medium, in a 96-well flat-bottom plate in an amount of 1.5×10^5 per well. After cultivation at 37℃ overnight, the medium was replaced by an EBM-2 medium containing 0.5% fetal calf serum (purchased from Chronetics), followed by cultivation for 24 hr. A solution of the test compound in dimethyl sulfoxide was added to each well, and the cultivation was continued at 37℃ for additional one hr. A human recombinant vascular endothelial growth factor (hereinafter abbreviated to "VEGF") was added to a final concentration of 50 ng/ml, and the stimulation of cells was carried out at 37℃ for 8 min. The medium was removed, the cells were washed with phosphate buffered saline (pH 7.4), and 10 μl of a solubilization buffer (Tris buffered saline (pH 7.4) containing 1% Triton X100, 2 mM sodium orthovanadylate, and 1 mM disodium ethylenediaminetetraacetate) was then added thereto. The mixture was shaken at 4℃ for one hr to solubilize the cells. An equal amount of Tris buffered saline containing 1% sodium laurylsulfate was added to and thoroughly mixed with the solution. This solution (2 μl) was adsorbed on a PVDF filter by dot blotting, and this filter was subjected to immunoblotting with anti-tyrosine phosphrylated MAPK antibory (purchased from Daiichi Pure Chemicals).

The level of phosphrylated MAPK was quantitatively determined with a densitometer, and the percentage phosphrylated MAPK in the presence of the test compound was determined by presuming the level of phosphrylated MAPK with the additon of VEGF in the absence of the test compound to be 100% and the level of phosphrylated MAPK in the absence of the test compound and VEGF to be 0%. The test compound concentration (IC_{50}) necessary for inhibiting 50% of the activation of MAPK was calculated based on the percentage of phophorylated MAPK.

[0156]

The results were as summarized in Table 1.

[00157]

[Table 8]

Table 1

Compound No.	IC_{50} (nM)	Compound No.	IC_{50} (nM)
1	1.8	33	3.5
4	2.1	34	4.2
5	2.9	35	3.7
7	5.2	36	3.3
8	11.0	37	2.3
9	5.1	40	12.0
10	7.8	41	4.9
11	15.0	42	5.9
13	2.2	43	3.8
14	0.7	45	2.0
16	2.9	46	4.3
17	11.0	47	4.0
18	0.6	48	0.5
19	0.6	49	4.3
20	8.5	50	0.5
21	3.4	52	4.4
22	0.4	53	5.9
23	5.4	54	0.5
24	0.6	55	2.8
25	3.9	56	5.1
26	5.3	57	6.5
28	4.0	58	5.1
29	4.4	59	5.8
30	1.7	62	16.0
31	2.5		
32	7.3		

[0158]

Pharmacological Test Example 2: Karyomorphosis test

A375 human melanoma cells (2×10^4) (obtained from Japanese Foundation for Cancer Research) were incolulated on a culture slide (manufactured by Falcon) and were cultured at 37℃. After the elapse of 5 hr from the initiation of the cultivation, the test compound was added to 10 μM and 1 μM, and the cultivation was continued for additional 48 hr. After the fixation of cells, 50 μg/ml propidium iodide solution containing

ribonuclease (200 μg/ml) was added to stain nuclei. The stained nuclei were observed under a fluorescent microscope to analyze the nuclei for abnormality of karyomorphosis. The change in karyomorphsis for test compounds was evaluated as (2+) when the change in karyomorphosis of cells took place at 1 μM; was evaluated as (+) when the change in karyomorphosis of cells took place at 10 μM; and was evaluated as (-) when the change in karyomorphosis of cells did not take place at 10 μM. The results were as summarized in Table 2.

[0159]

[Table 9]

Table 2

Compound No.	Change in morphosis	Compound No.	Change in morphosis
13	(-)	37	(-)
14	(-)	38	(-)
15	(-)	39	(-)
16	(-)	40	(-)
17	(-)	41	(-)
18	(-)	42	(-)
20	(-)	43	(-)
21	(-)	44	(-)
22	(-)	45	(-)
24	(-)	46	(-)
25	(-)	47	(-)
26	(-)	48	(-)
28	(-)	49	(-)
29	(-)	52	(-)
30	(-)	53	(-)
31	(-)	55	(-)
32	(-)	58	(-)
33	(-)	59	(-)
34	(-)	60	(-)
35	(-)	61	(-)
36	(-)	62	(-)

[0160]

Pharmacological Test Example 3: Antitumor effect on human glioma cells (GL07)

Human glioma cells GL07 (obtained from Central Laboratories for Experimental Animals) were transplanted into nude mice. When the tumor volume

became about 100 mm^3, the mice were grouped. In this case, grouping was carried out so that each group consisted of four mice and the average tumor volume was even among the groups. The test compound was orally or intraperitoneally administered at a dose of 20 mg/kg to the test groups every day once a day for 9 days, while the medium was administered to the control group in the manner as in the test groups. The tumor growth inhibition rate (TGIR) was calculated as follows: The tumor growth inhibition rate (TGIR) = $(1 - Tx/Cx) \times 100$ wherein Cx represents the volume of tumor at day x for the control group when the tumor volume at the day of the start of the administration was presumed to be 1; and Tx represents the volume of tumor for test compound administration group.

[0161]

The tumor growth inhibition rate for representative examples of a group of compounds according to the present invention in shown in Table 3.

[0162]

[Table 10]

Table 3

Compound No.	Administration site	Tumor growth inhibition rate (%)
4	Oral	61
5	Oral	59
9	Intraperitoneal	59
14	Intraperitoneal	81
16	Intraperitoneal	77
17	Intraperitoneal	85
18	Oral	57
24	Oral	63
25	Intraperitoneal	68
28	Intraperitoneal	84
29	Oral	64
48	Interperitoneal	90
50	Oral	59
51	Oral	65
54	Oral	59
62	Oral	78

ABSTRACT

[Summary]

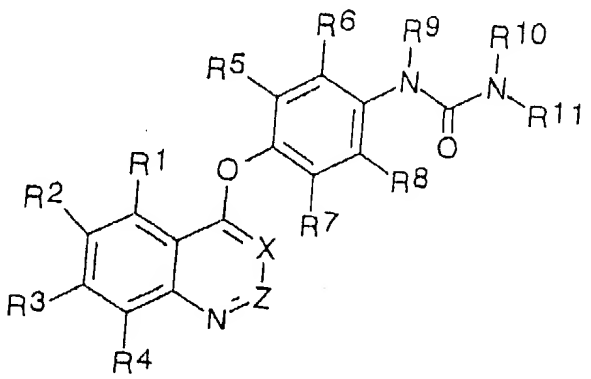
[Object]

An object of the present invention is to provide compounds which have antitumor activity and do not change cyromorphosis.

[Means to Solve Problems]

Compound represented by formula (I) below.

[Chemical Formula 1]



(I)

wherein X and Z each independently represent CH or N;

R^1 to R^2 represent H, alkyl, alkoxy, alkenyl, alkynyl, nitro, or amino;

R^4 represents H;

R^5, R^6, R^7, and R^8 represent H, halogen, alkyl, alkoxy, alkylthio, nitro, or amino;

R^9 and R^{10} represent H or alkyl; and

R^{11} represents alkyl, alkenyl, alkynyl, or aralkyl.

[Selected Drawing]

None